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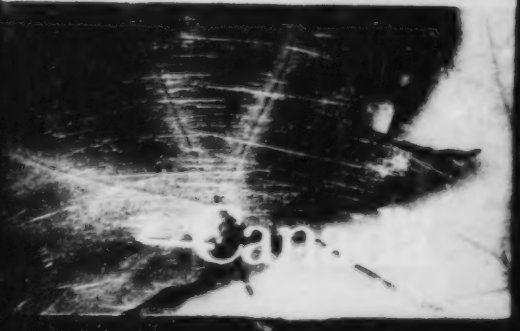
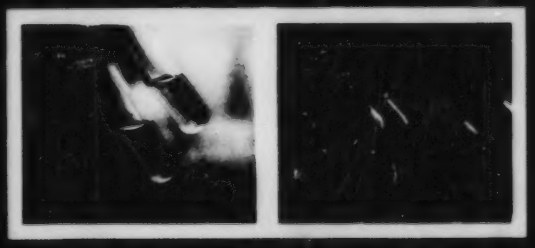
Follow the Leaders



FOLLOW THE LEADERS

Virus research that lets persons with HIV/AIDS lead productive lives. Molecular science that draws medicinal and industrial products from natural, renewable resources. Protein investigation that probes beneath the surface of genomic discovery.

Behind each of these novel ideas stands a Canadian who is out front, exploring the promise of biotechnology on the frontiers of human knowledge.



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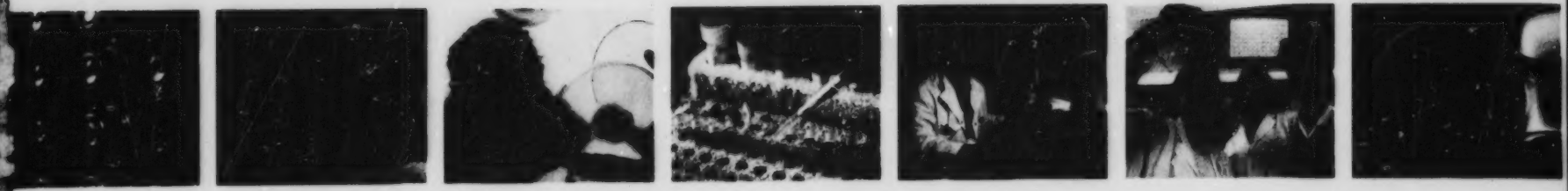
Follow the Leaders

CANADIAN INNOVATION IN BIOTECHNOLOGY



The Government of Canada is proud to present the stories that highlight how Canadian innovators are touching lives, generating economic benefit, and laying foundations for future discovery. Stories that demonstrate why… Canada is a great place to bring innovation to life.

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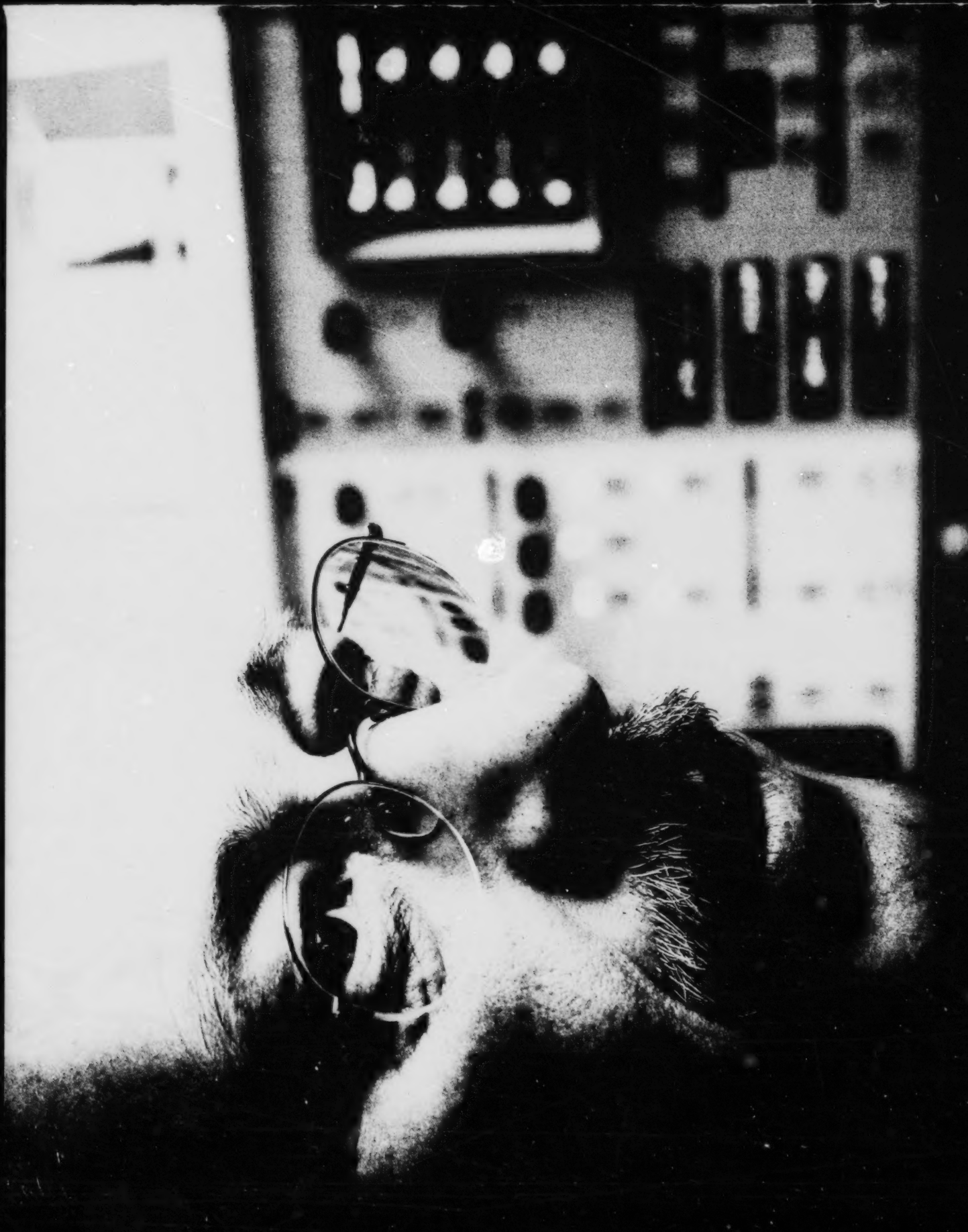
"Humans have about 30,000 genes
and 99.9 per cent of them are identical.
That means that only one chemical letter in a thousand
is different in the genome of say, your neighbour and Albert Einstein."

DR. HENRY G. FRIESEN,
CHAIRMAN, GENOME CANADA



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CANADA:
A GLOBAL LEADER
in Biotech

Last year, scientists around the world finished mapping the human genome, ushering in a new era of scientific discovery. Canada played a major role in that achievement. As part of the global team that worked on the Human Genome Project, Canadian scientists were proud contributors to one of the most fascinating and promising discoveries in human history. Today, as we explore how this new knowledge will change our lives, Canada remains a leader in the field of scientific discovery.

In Canada, scientific breakthroughs seem to happen almost daily. In the not-so-distant future, we will see vaccines for cancer, cures for diabetes and AIDS, regeneration of spinal cords, and food enriched for nutritional and medicinal purposes. The enabling power of biotechnology promises to create entirely new approaches to feeding ourselves and our children, treating illnesses and disease, and providing a sustainable supply of renewable raw materials and energy for economic development.

At the same time, Canada understands that the pace of change in this field demands an increased responsibility on the part of government to ensure that biotechnology is used wisely and safely—to strike an appropriate balance between the detection and management of risk and the development of new discoveries.

Despite recent economic downturns, biotechnology in Canada continues to grow. With research and development funding projected to reach more than $1.7 billion in 2002, and industry revenues expected to reach more than $5 billion, the biotech sector is an important part of the foundation of a diversified economy.

The Government of Canada is dedicated to seeing Canada become one of the top five countries in the world for biotech research and development by 2010. This commitment is helping to energize our industry, which is gaining increased levels of research investment from both the private and public sectors. The Canada Foundation for Innovation, a creation of the federal government, has announced funding of $1.55 billion for Canadian universities and research institutions. Combined with private-sector partnerships, we now have capital investments of almost $3.9 billion to strengthen the biotechnology research environment.

Canadian universities are also rising to the challenge of making Canada a global leader in biotech research. Programs that are designed specifically to grow in partnership with government and industry are continuing their long history of excellence in research. To help train the scientists of tomorrow, more academic programs are providing legal, business management and marketing skills to support both the scientific practice of biotechnology and the commercialization of innovations. As the science of biotech advances, so do the requirements that are placed on its practitioners. The biotech industry continues to meet these unique demands as it moves more products into the marketplace.

Indeed, Canada is now a global 'hot bed' for biotechnology. Organizations such as Genome Canada and the National Research Council of Canada are leading projects that collectively involve thousands of researchers with a wide range of scientific expertise, resulting in approximately 17,000 biotech products or processes currently in the pipeline for development. In its 2002 world study, *Competitive Alternatives: Comparing business costs in North America, Europe and Japan*, KPMG cited Canada, for the third consecutive time, as both the lowest-cost industrialized country for conducting business and the number one country in which to conduct biomedical research and development.

Canadians are already reaping the benefits of biotechnology and the powerful results of collaboration in this sector. Over the next decade or two, biotechnology will change our world in ways only limited by our imagination. Canada's commitments to fostering innovation and attracting investment will ensure that Canada delivers biotechnology to the world.

ALLAN ROCK,
MINISTER OF INDUSTRY

PIERRE S. PETTIGREW,
MINISTER FOR INTERNATIONAL TRADE

Canada...the right place to bring biotechnology to life

SUCCESS IN BIOTECHNOLOGY DEMANDS THE RIGHT BLEND OF TALENT, CREATIVITY AND OPPORTUNITY—A MIX EASILY FOUND IN CANADA. BOASTING ONE OF THE WORLD'S BEST FISCAL ENVIRONMENTS, PROVEN LOW BUSINESS COSTS, A TALENTED AND DEPENDABLE WORK FORCE, AND A BUSINESS AND REGULATORY ENVIRONMENT COMMITTED TO FOSTERING SUCCESS WHILE PROTECTING THE PUBLIC INTEREST, IT'S NO WONDER CANADA IS HOME TO MANY OF THE WORLD'S TOP BIOTECHNOLOGY RESEARCHERS AND FIRMS.

AS THE WORLD FORGES AHEAD INTO THE 21ST CENTURY, CANADA IS STAKING ITS CLAIM AS A COUNTRY WITH ENORMOUS POTENTIAL TO LEAD THE WAY IN KEY AREAS OF BIOTECHNOLOGY: HUMAN AND ANIMAL HEALTH, AGRICULTURE AND THE ENVIRONMENT, GENOMICS AND PROTEOMICS. IN FACT, CANADA IS ALREADY HOME TO THE SECOND-LARGEST NUMBER OF BIOTECHNOLOGY COMPANIES IN THE WORLD. AND THOSE COMPANIES ARE ALREADY CAPTURING WORLD MARKETS IN EVERYTHING FROM MEDICAL DEVICES AND BIOINFORMATICS, TO ENVIRONMENTAL ASSAYS AND INDUSTRIAL PROCESSES.

THE SECRET IS OUT

KPMG recently released a report comparing international business costs, which confirmed that Canada is the world's most cost-competitive country. But that's only one aspect of an incredible range of benefits. In reality, what sets Canada apart is its combined advantages in scientific expertise, a balanced economy projected to weather the current economic storm, access to U.S. markets, and low labour and production costs. Add an excellent quality of life and a world-respected regulatory system, and it's not hard to see why Canada is one of the best places in the world to do business in biotechnology.

SCIENTIFIC EXPERTISE

Canada has cornered the market when it comes to the greatest asset in a knowledge economy: people. With the highest percentage of post-secondary graduates, Canada offers an exceptionally high ratio of skilled workers. Still, the Government of Canada believes it can improve an already good situation. The recently announced innovation strategy provides a vision for improved access to higher learning, knowledge on-line, and the ability to gain new skills. Considering that Canada already has the highest percentage of population with Internet access among G-8 countries, it's no wonder Canada's workforce is considered a valued asset.

The future of science and technology is both highly specialized and necessarily multi-disciplinary. To support such demands, the Government of Canada established the Canada Foundation for Innovation (CFI). An independent corporation, the CFI's goal is to strengthen the capability of Canadian universities and research institutions to carry out world-class research and technology development. The CFI targets its investments in research infrastructure projects in health, science, engineering and the environment. These projects help improve the quality of life of Canadians. They also help protect the environment. Advances in many areas of science translate into potential economic growth. Since 1997, the CFI has supported 1,975 projects at 102 Canadian universities, colleges, hospitals and not-for-profit research institutions.

Canada also recognizes that talent is located all over the world. Researchers from around the globe are welcome to come to Canada to explore new ideas and opportunities in a dynamic environment. Canada's fast-track immigration system for skilled workers helps universities and firms attract top talent and grow their core competencies. A diversity of culture and depth of knowledge are key factors in understanding and responding to global and niche needs.

INDUSTRY SUPPORT

Recognizing biotechnology's vital role in the future, Canada has established an innovation system supporting collaboration between scientific and business communities. The Networks of Centres of Excellence (NCE) program fosters powerful partnerships between university, government and industry to develop Canada's economy

and improve the quality of life for Canadians. World-class, regional technology clusters support the growth of significant concentrations of innovative companies around R&D facilities such as those found in universities or leading-edge government laboratories.

Montréal, home to firms such as Neurochem and Nexia, hosts the world's largest cluster of pharmaceutical research and development organizations. The bio-agriculture cluster in Saskatoon, home to VIDO, continues to attract interest and investment from all corners of the globe. Toronto's medical research community ranks among the top four in North America, attracting firms such as Aventis Pasteur and researchers such as Dr. Lap-Chee Tsui.

These successes reflect a key fact: Canada understands the corporate sector's need to keep an eye on the bottom line. Amongst G-8 nations, Canada's tax credits for research and development are among the most generous—with no less than 20 per cent credit provided for all eligible expenditures. A recent $100 billion tax reduction plan will see personal income taxes fall by 35 per cent and corporate business tax rates drop to 5 percentage points below those in the United States. A highly efficient regulatory system helps companies bring products to market faster, while Canada's 20-year patent protection plan ensures they realize rewards over an extended period. In addition to low labour and production costs, Canada's first-rate telecommunications infrastructure helps reduce the everyday costs of doing business in a global market.

Through the North American Free Trade Agreement (NAFTA), Canada has paved the way for domestic companies to gain direct access to vital sectors of the massive U.S. market. In fact, Canada is already the largest U.S. trading partner with the total value of Canada-U.S. trade now standing at $676 billion per year.

QUALITY OF LIFE

Canada has an enviable reputation for repeatedly capturing the United Nation's designation as one of the best countries in the world in which to live. In addition to offering an acclaimed healthcare system, superior universities and safe communities, Canada enjoys the lowest cost of living among G-8 nations. It all adds up to making Canada a great place to work and to live.

NET RESULTS

Canada's many benefits make it possible for this country to develop, attract and retain the best and brightest minds, the most innovative entrepreneurial spirits, and the most savvy investors.

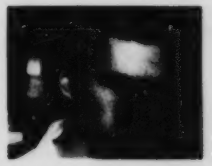
This book provides a snapshot of Canadian Innovation in Biotechnology at a critical point in time—the beginning of a new century in which technological advances are heralding the next industrial revolution. Read the stories of some of our most prominent and innovative scientists and business leaders and see for yourself why Canada is such a great place to bring innovation to life.

HEALTH

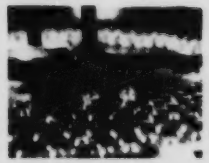
AS THE 21ST CENTURY UNFOLDS, THE HEALTH SECTOR IS EMERGING AS THE LARGEST AND MOST IMPORTANT DRIVER OF THE GLOBAL ECONOMY. SOME INDUSTRY ANALYSTS PREDICT THAT THE GROWTH RATE IN HEALTH-RELATED KNOWLEDGE IN THE CENTURY AHEAD WILL EXCEED THE GROWTH RATE THAT THE INFORMATION TECHNOLOGY SECTOR EXPERIENCED IN THE 20TH CENTURY. IN FACT, SUCH PREDICTIONS ARE THE LOGICAL ENDPOINT OF THE RECENT CONVERGENCE OF HEALTH SCIENCE AND INFORMATION TECHNOLOGY, WHICH IS DRIVING RECENT ADVANCES IN BIOTECHNOLOGY.

TODAY, CANADA'S BIOTECHNOLOGY SECTOR IS THE SECOND LARGEST IN THE WORLD. CANADIAN HEALTH RESEARCHERS ARE BRINGING BETTER HEALTH FOR ALL CANADIANS AND PEOPLE AROUND THE WORLD. IN THE PROCESS, THEY ARE CONTRIBUTING TO ECONOMIC DEVELOPMENT THROUGH COMMERCIALIZATION AND JOB CREATION, AND GENERATING SIGNIFICANT RETURNS FOR INVESTORS.

CANADIAN INNOVATION IN HEALTH BIOTECHNOLOGY



In the 1920s, Canadian scientists brought insulin injections to the world. Now, they're revolutionizing diabetes treatment again. A University of Alberta team has successfully transplanted islets (the cells that produce insulin) offering diabetics a new lease on life.



Apoptosis is the process of cellular self-destruction. But cancer cells never self-destruct. Dr. Tak W. Mak believes if researchers can determine why cancer cells are immune to apoptosis, they may find ways to reactivate it.

Millenium Biologix Inc. was launched in 1993 to develop and market Skelite™, a skeletal repair material. Skelite is used as implantable bone grafts and tissue engineering scaffolds on earth, and has also been tested in space by NASA to learn why micro-gravity induces bone density loss.

A pioneer in photodynamic therapy, Vancouver-based QLT has shepherded two light-activated drugs through clinical trials: Photofrin, which is effective against lung, bladder, cervical and esophageal cancers; and Visudyne®, which helps maintain the vision of patients with age-related macular degeneration (AMD).

Aventis Pasteur is harnessing the canarypox virus in experimental vaccines designed to boost the human immune system against cancer. Unlike traditional vaccines, these vaccines aim to defeat (treat) cancer rather than prevent it.

Dr. Mark Wainberg was the first Canadian scientist to isolate the AIDS virus, and his lab was the first to demonstrate the anti-viral properties of the breakthrough drug 3TC. Today, he's searching for new angles of attack against AIDS.

The world is in the midst of a profound revolution in health research—a revolution driven by the rapidly emerging understanding of the molecular basis of life. As with prior scientific revolutions, this one draws upon the convergence of diverse disciplines.

As genetics, molecular biology, small molecule and surface chemistry uncover new areas of discovery, information technology makes it possible to collect, store and analyse enormous volumes of data. As well, epidemiology, health economics, bioethics and the humanities provide the impetus to consider new developments from both individual and global perspectives.

Historically recognized throughout the world for scientific excellence, Canadian health researchers play a key role in this revolution. In a very real sense the biotechnology revolution started in 1921, when Canadian researchers Dr. Frederick Banting and Charles Best discovered insulin, showing that a protein could be used as a new therapeutic. Recently, Dr. Ray Rajotte and his University of Alberta team pioneered the 'Edmonton Protocol', eliminating the need for insulin injections in some people with Type I diabetes. In the emerging fields of genomics and proteomics, Canadians are demonstrating their leadership in areas such as cell signaling, developmental biology, and bioinformatics. For example, the work of Dr. Tony Pawson, one of the world's leading experts in cell circuitry and proteomics, provides a foundation for novel approaches to drug discovery in the 21st century.

It is clear that advances in human and animal health will be realized by integrating current knowledge with multi-disciplinary expertise. The accelerating pace of the health research revolution is driven by significant global commitments—of both human and financial capital—from the public and private sectors. The Government of Canada understands that success in the commercial arena depends on public investment in health research and innovation.

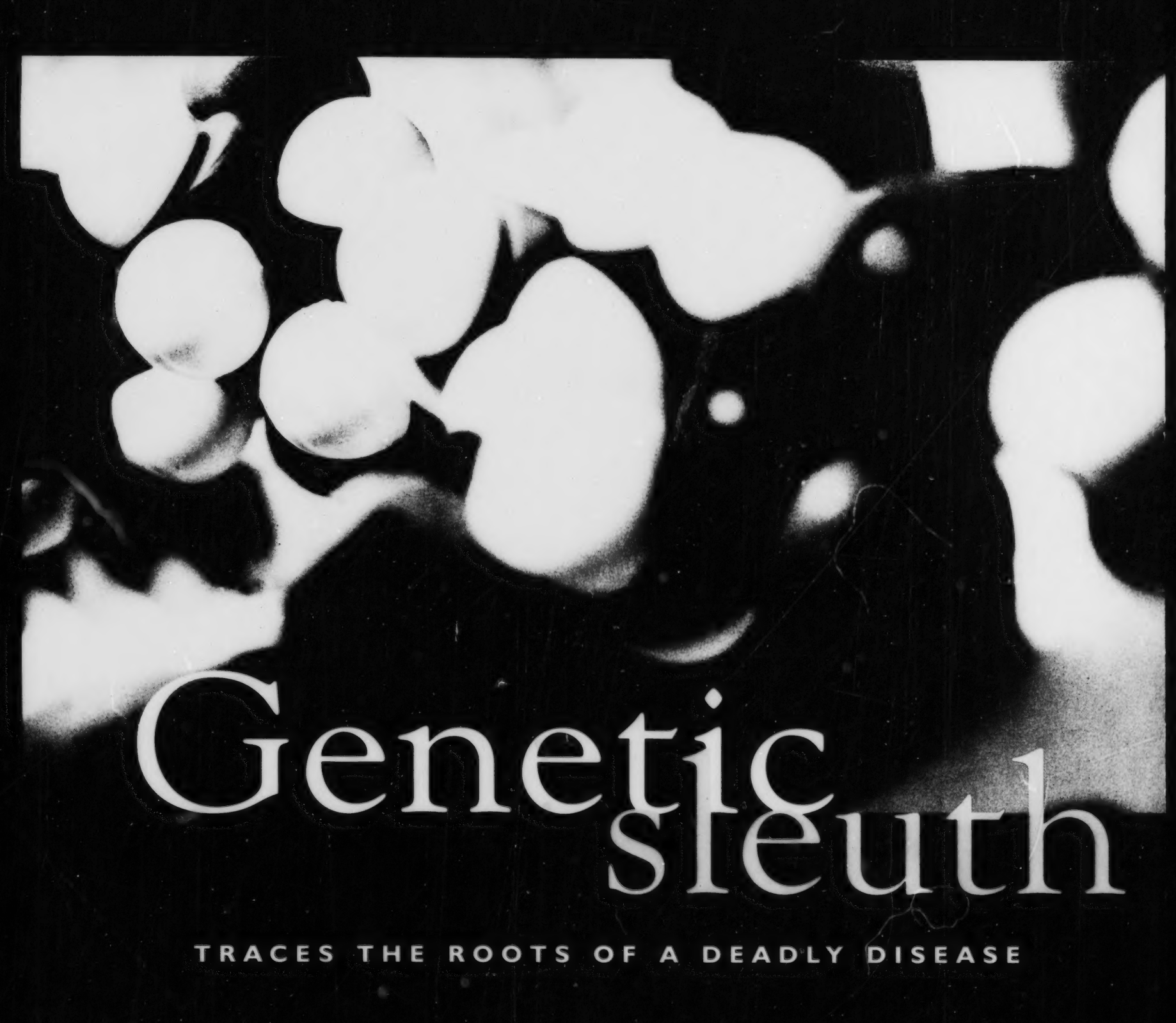
Through the Canadian Institutes of Health Research (CIHR), the federal government is leading the way in establishing a national health research agenda and funding academic health research. CIHR's objective is to excel in the creation of new knowledge and its translation into improved health, more effective health services and products, and a strengthened Canadian healthcare system. Through 13 'virtual' Institutes, CIHR embraces four pillars of research: biomedical science; clinical research; health services and systems; and the social, cultural and other determinants of health.

The Networks of Centres of Excellence of Canada (NCEs) further enhance Canada's health research infrastructure. Each NCE links scientists from across the country, allowing collaboration on research in areas such as arthritis and stroke, genetic and bacterial diseases, vaccines and immunotherapies, protein engineering and stem cells.

The Canada Foundation for Innovation (CFI) strengthens the research capacity of Canadian universities, colleges, research hospitals, and other not-for-profit institutions. CIHR and the CFI—in partnership with the Social Sciences and Humanities Research Council of Canada and the Natural Sciences and Engineering Research Council of Canada—established the Canada Research Chair Program to help universities and research hospitals hire and retain world-renowned researchers to foster new discoveries and learning. Genome Canada is developing and implementing a national strategy in genomics research. In addition, Technology Partnerships Canada encourages private-sector investment in innovative biopharmaceutical R&D.

These programs are part of the Government of Canada's commitment to make Canada one of the top five countries in the world investing in R&D. They also seek to create strong ties between research organizations, universities and industrial partners, facilitating the translation of research discoveries into health benefits and economic gain.

Canada provides an exceptional environment for scientific enquiry and innovation in health research, and a regulatory system acknowledged as one of the best anywhere. To conduct scientific research in Canada is to make a statement of excellence. We invite you to take a closer look at what Canada offers as a home for health research that is paying both health and economic dividends.



Genetic sleuth

TRACES THE ROOTS OF A DEADLY DISEASE

DR. LAP-CHEE TSUI'S RESEARCH ON GENETIC MUTATIONS BRINGS MAJOR BREAKTHROUGHS IN THE FIGHT AGAINST CYSTIC FIBROSIS.

Cystic fibrosis (CF) is the most common genetic disease among Caucasians, affecting one in 2,500 children. People with CF are missing part of the genetic instructions that control the viscosity of mucous in the lungs, airways and pancreas. Their mucous is thick and sticky, making it difficult to breathe, and creating an ideal environment for bacterial growth. Most children with CF die in childhood or young adulthood from heart or lung complications.

Dr. Lap-Chee Tsui's discovery of the gene that causes cystic fibrosis has given researchers a starting point for understanding the disease, and developing possible treatments.

The human genome includes approximately 35,000 different genes. For Dr. Lap-Chee Tsui, Geneticist in Chief of the Genetics and Genomic Biology Program at Toronto's Hospital for Sick Children, tracking the cystic fibrosis gene was like looking for a particular house without even knowing what continent it was on.

"First, we had to narrow down the search to a region of the genome," he says. In 1985, together with Dr. Manuel Buchwald and Collaborative Research Inc., Dr. Tsui identified the first DNA marker linked to CF on chromosome 7, one of the 23 chromosome pairs that carry the human genetic code. "It was like finding the city where the gene should be," says Dr. Tsui. "But it still wasn't clear exactly on which street—or region of the stretch of DNA—the gene would be located."

Dr. Tsui is one of Canada's foremost geneticists. A holder of five honorary doctoral degrees who earned his Ph.D. from the University of Pittsburgh, he has devoted the past 21 years to studying cystic fibrosis. In 1989, when Dr. Tsui and his team finally isolated the gene that codes for CF, the discovery brought international attention to Canada's genomic research, and fresh hope in the search for treatments.

But locating the gene wasn't enough—researchers still didn't know where the mutation was. "Once you find the gene, you need to find out what's wrong with it," says Dr. Tsui. "It's like entering a house—you have to turn on the lights and see if the switch is defective, or try the doorknobs to see if they work."

MAPPING CHROMOSOME 7

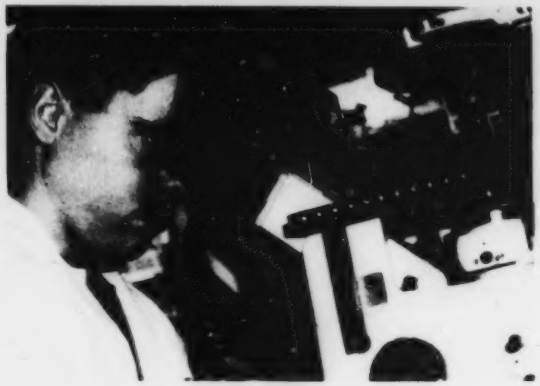
At the Centre for Applied Genomics in Toronto's Hospital for Sick Children, researchers are connecting the dots between genes on chromosome 7 and the diseases that they cause. "Chromosome 7 contains 5 per cent of the human genome," says Dr. Lap-Chee Tsui, the Centre's Director. "There are about 5,000 different diseases originating in the genome, so approximately 250 of them could be associated with chromosome 7."

The research, which receives funding from Genome Canada, is a vital part of the Human Genome Project—a global effort to map the entire human genome and, ultimately, understand the roots of disease. "Canada has contributed five to ten per cent of the genetic mapping," says Dr. Tsui. "The kind of work we do is the backbone of the Human Genome Project."

A TINY BUT DEADLY MUTATION

The cystic fibrosis gene sits on the 'long arm' of chromosome 7. This region includes 230,000 base pairs of DNA that spell out the instructions for the 1,480 amino acids in the protein CFTR—cystic fibrosis transmembrane conductance regulator. CFTR controls the flow of chloride ions through cell membranes of mucous-producing cells in the stomach, lungs, nose and pancreas.

In 1989, Dr. Lap-Chee Tsui, together with Dr. Jack Riordan and Dr. Francis Collins, discovered that most people with CF are missing just 3 of the 230,000 base pairs in this region of the chromosome. That translates into one missing amino acid, a tiny mutation that is enough to disrupt the flow of chloride ions. When the chloride can't flow properly, mucous becomes thick and sticky, causing deadly cystic fibrosis.



After months of non-stop research, Dr. Tsui's team located one such defect: most CF patients are missing three base pairs, or units of DNA, from their genetic code. This loss affects the protein CFTR—cystic fibrosis transmembrane conductance regulator—which regulates the flow of chloride ions through cell membranes.

This defect produces 70 per cent of CF cases. The other 30 per cent are caused by more than a thousand other mutations in the same gene. Since 1989, Dr. Tsui's research has focused on gaining a better understanding of the CF gene's role in the body, and on identifying additional mutations.

And the picture gets even more complicated, because not all defective genes are equal. "Some patients do better than others, even with the same mutation," says Dr. Tsui. The severity of CF is affected by 'modifier' genes, which may provide genetic instructions for other ways of regulating ion flow. "Or it could be a totally unknown mechanism," he says. "We are studying the modifier genes, but we can't start with any preconceived notion of what those genes do."

Many researchers are looking for ways to correct the ion channel defect that causes most cases of CF. One possible approach is to locate and open up other ion channels in the cell. Another is to reactivate the defective protein. "People are working on various types of small molecules that could do this," says Dr. Tsui.

This kind of genetic research is now much easier thanks to the Human Genome Project, which aims to characterise all the genetic information in human cells. The project helps by identifying candidate genes, so researchers such as Dr. Tsui have a more focused starting point. "We just need to test whether those genes are suitable candidates," he says.

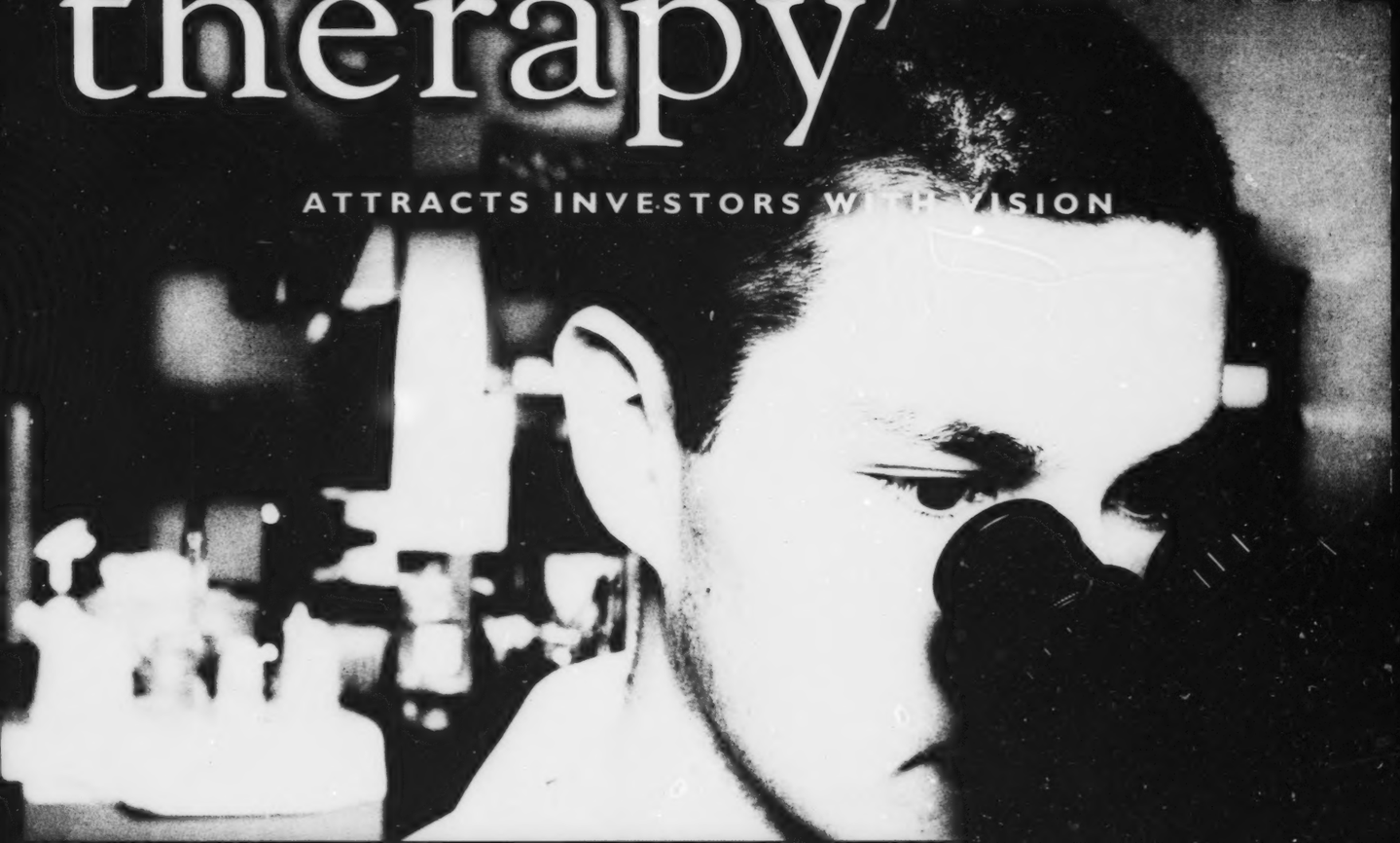
In the future, Dr. Tsui hopes that geneticists will be able to put a genetic face to the name of every human disease. "My wish is to be able to provide the genetic basis for most, if not all, of the diseases that affect us."

Canada has a very rich culture in medical research. We have solid data on patients, very good diagnoses and a strong collegial spirit among researchers. I find this kind of working environment excellent for the large-scale studies that we do.

DR. LAP-CHEE TSUI,
GENETICIST IN CHIEF OF THE GENETICS
AND GENOMIC BIOLOGY PROGRAM,
TORONTO'S HOSPITAL FOR SICK CHILDREN

Photodynamic therapy

ATTRACTS INVESTORS WITH VISION



DR. JULIA LEVY, MOLECULAR BIOLOGIST TURNED BUSINESS MAVERICK, PUTS QLT INC. INTO THE SPOTLIGHT.

One could say Quadra Logic Technologies' success began when Dr. Julia Levy noticed that her son sometimes had a strange rash after playing in nearby fields. A colleague suggested that it could be caused by a toxic enzyme found in cow parsley—an enzyme that is inactive unless struck by sunlight.

Dr. Levy began to think about using light wavelengths to activate drugs. In 1987, six years after forming QLT with a group of colleagues, the company acquired the rights to Photofrin—a light-activated cancer drug. The company shepherded the drug through clinical trials, and made it the first photodynamic therapy to hit the market.

By then, Dr. Levy had turned her attention to another family member and a much more serious condition, which ultimately led to a medical breakthrough and even greater success for QLT.

Dr. Julia Levy knew little about age-related macular degeneration (AMD) before 1985, the year her mother began to go blind. At the time, QLT—a company she helped found four years earlier—was focused on cancer treatment.

"But when your parent is losing her vision, especially when you're a scientist, you become very aware of a disease," she says. A year later, she heard an ophthalmologist hypothesize that photodynamic therapy (PDT)—QLT's specialty—could treat tumours in the eye. Dr. Levy immediately made the connection between PDT and AMD.

"My peripheral vision was 20-20," she says. By 1994, that vision had culminated in clinical trials of a new drug: Verteporfin, now marketed as Visudyne®.

For the AMD patient, this photodynamic therapy is a 20-minute process that begins with a pinprick. After an intravenous injection, the drug quickly travels through the bloodstream, adhering preferentially to the walls of abnormal blood vessels such as those in the damaged retina. Fifteen minutes later, an ophthalmologist delivers an 83-second burst of non-burning laser light to activate the drug, thereby converting normal oxygen in the cell into a highly energized form called 'toxic singlet oxygen'. The singlet oxygen immediately disrupts normal cellular functions, causing targeted cells to curl into unusual shapes—a reaction known as 'beading'. This transformation tricks the body into thinking that the vessel is about to hemorrhage.

PHOTOFRIN'S SUCCESS SUPPORTS LONG-TERM GROWTH

Dr. Julia Levy founded Quadra Logic Technologies (QLT) Inc. in 1981 along with three fellow University of British Columbia researchers—Jim Miller, John Brown and Tony Phillips—as well as Ron McKenzie, a friend with an MBA. The company initially focused on antibody research, but soon shifted its attention to photodynamic therapy (PDT).

In 1987, QLT bought a subsidiary of Johnson & Johnson and acquired the rights to Photofrin, a light-activated cancer drug. QLT shepherded Photofrin through clinical trials that led to its approval for treatment of lung, bladder, cervical and esophageal cancers.

In June 2000, QLT sold its Photofrin rights to Axcan Pharma Inc. for almost $US540 million, thereby leveraging the world's first PDT success to support its own long-term research and development projects.

AMD: FACTS AND FIGURES

Age-related macular degeneration (AMD) is the leading cause of blindness among men and women over 50 years of age, striking an estimated 500,000 new victims worldwide every year.

Wet AMD—the condition's more severe form—results from the growth of abnormal blood cells across the macula, or central area of the retina. These blood vessels progressively leak fluid and create scar tissue. Within months, the sight of AMD sufferers starts to deteriorate, becoming increasingly foggy in the centre of their field of vision.

Without treatment, AMD invariably leads to blindness.

Seeking to avoid a rupture that could damage surrounding tissue, the body quickly destroys the distressed cell.

Because plenty of healthy blood vessels remain to nourish the retina, destroying these abnormal blood vessels does not harm vision. Rather, the therapy effectively eliminates the risk of abnormal cells leaking excess protein or forming scar tissue, the two processes that damage the retina in AMD.

While Visudyne grew from an innovative idea to an effective therapy, Dr. Levy embraced a personal transformation. After two brief stints as QLT's interim CEO, she formally took over as President and CEO in 1995.

We've built an organization that has proven it can successfully take a product from the bench to the market—not once, but twice. And we are eager to do it again.

DR. JULIA LEVY, PRESIDENT AND CEO OF QLT INC., 1995-2002 (VANCOUVER, B.C.)

Under Dr. Levy's stewardship, Visudyne underwent worldwide clinical trials. The results were superb. One year after treatment, 60 per cent of AMD patients showed treatment benefit; in fact, approximately 20 per cent experienced improved vision. Virtually all the patients receiving the photodynamic therapy faired better than AMD sufferers who received no treatment. In a four-year follow-up, many recipients enjoyed complete stabilization of their vision.

Visudyne received full regulatory approval for the treatment of predominantly classic AMD in 2000 and has since been used to treat more than 150,000 people worldwide. QLT expects

sales of the drug to reach US$275 to $300 million in 2002. More recently, the drug was approved for treating abnormal retinal blood vessels in patients with pathologic myopia and ocular histoplasmosis syndrome.

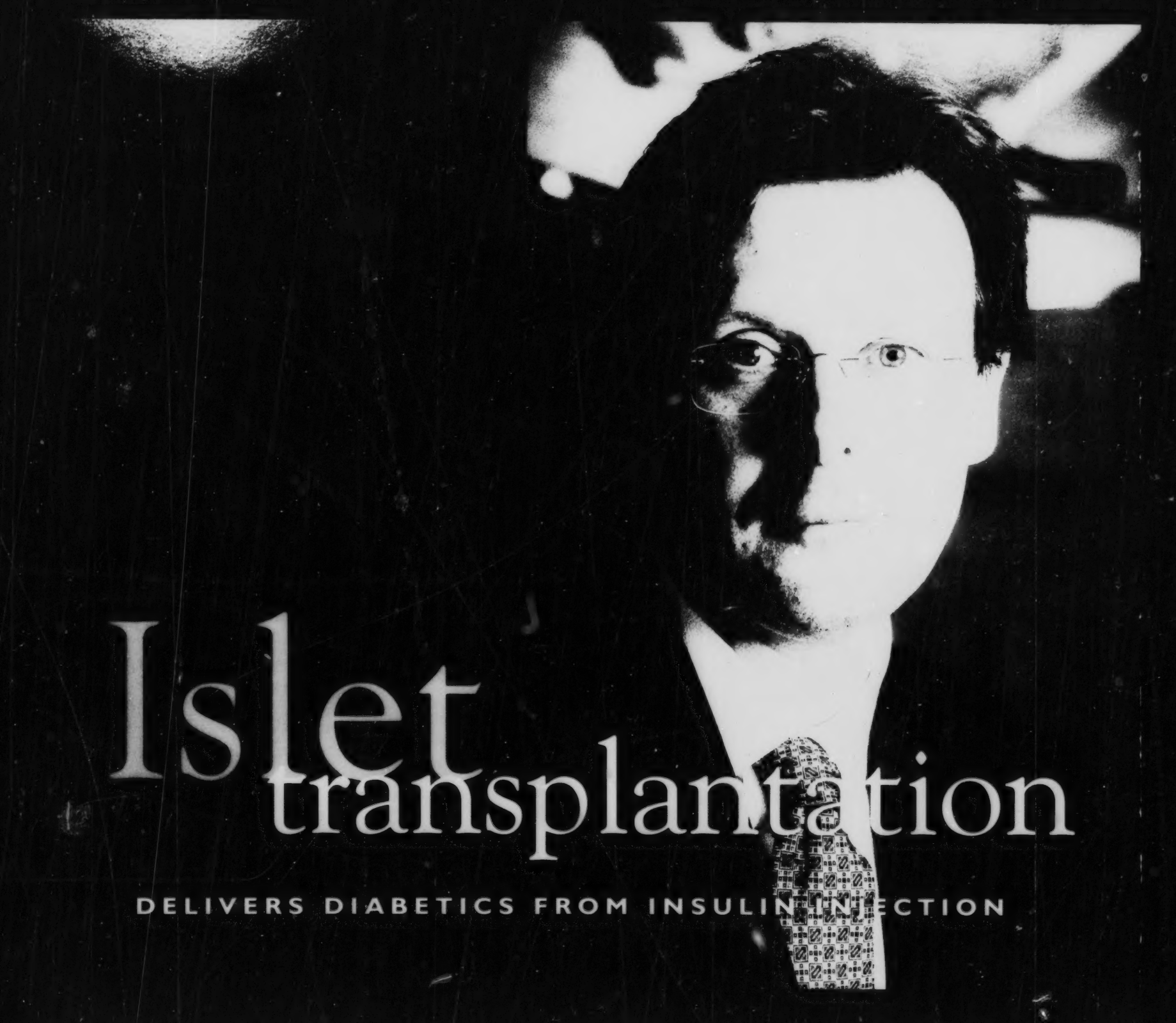
Visudyne's success has propelled QLT into an elite class—making it one of only a handful of biotech companies in North America to operate at a profit. After successfully taking not one but two products from bench to market, Dr. Levy hopes QLT will spur other Canadian researchers to turn their work into clinical and commercial success. She believes that academic research in Canada is "first rate, absolutely the best in the world," but that too many researchers turn their ideas over to U.S. or European firms to develop into commercial products.

"In the past, the only option that Canadian scientists had was to be like we are with our natural resources: selling off our raw resources cheap, while someone else reaps the economic benefit," she says. "Why should we continue to do that?"

The Vancouver region is now home to more than 100 biotech companies, and QLT's success has generated a lot of optimism. In February 2002, Dr. Levy stepped down as CEO to become the Executive Director of QLT's Scientific Advisory Board. Eager to use her experience to help the Canadian biotech industry reach a critical mass, she now sits on the boards of several young firms. She calls herself a glorified talent scout, looking out for the "next blockbuster" for QLT to develop, license or acquire.

A former graduate student once said of Dr. Levy: "If a bag of garbage were dumped in front of her with a diamond hidden in it, she'd find the diamond right away." No doubt more success is on the horizon.

Dr. Julia Levy's reputation spans research excellence and business acumen. Her success in leading QLT to profitability garnered the 1998 *Pacific Canada's Entrepreneur of the Year Award.*


Islet
transplantation
DELIVERS DIABETICS FROM INSULIN INJECTION

BIOMEDICAL ENGINEERING, PHYSIOLOGY AND TRANSPLANT SURGERY CONTRIBUTED TO THE EDMONTON PROTOCOL—A NOVEL TREATMENT THAT ELIMINATES INSULIN DEPENDENCY.

For the second time in medical history, a diverse team of Canadian scientists is revolutionizing diabetes treatment.

The insulin injection arose from canine experiments conducted by physician Frederick Banting and medical student Charles Best, under the supervision of University of Toronto professor J.R.R. Macleod. But it was James Collip, a visiting biochemist from Edmonton, who isolated a pure enough 'dose' of the hormone to perform the first successful treatment.

Just footsteps from Dr. Collip's old lab at the University of Alberta, another team of disparate scientists has pooled their expertise to successfully transplant islets—the cells that produce insulin. Unlike an injection regimen, which only postpones the ravages of the disease, the Edmonton Protocol gives diabetics a new lease on life.

It takes a lot of determination to stick to your convictions when a paltry 8 per cent of patients realize any benefit from your efforts. But with diabetes, the alternative—a slow and painful system shutdown—is unacceptable. And so it is that Dr. Ray Rajotte at the University of Alberta has spent almost 30 years working in the area of islet transplantation—the most physiological way to give insulin to a diabetic patient.

Type I diabetes is the end result of an immune system attack on islets—specialized cells in the pancreas that produce insulin. The body needs this hormone to convert food into energy. Without it, sugars pile up in the bloodstream and are eliminated through the kidneys while tissues throughout the body starve to death.

At best, Type I diabetes can be managed through insulin injections and a strict diet. At worst, it leads to serious complications such as kidney failure, blindness, nerve damage, heart attack, and stroke. But best always deteriorates to worst: on average, diabetes cuts 15 years off a person's lifespan. Type II diabetes, in which the body produces insulin but uses it poorly, is less severe and more manageable but still reduces quality of life.

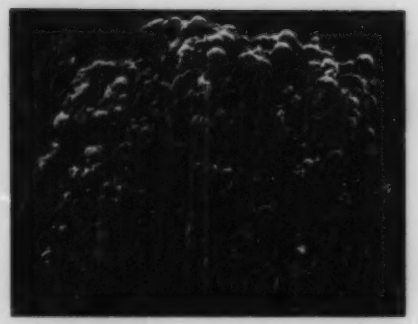
To a biomedical engineer such as Dr. Rajotte, the concept of replacing the broken part in the insulin production plant seemed an obvious

BIRTH OF A NEW RESEARCH CENTRE

The University of Alberta will soon be home to a new institute that plans to tackle all aspects of diabetes treatment. The success of the islet transplant team helped the university win CAD$11.5 million from the Canada Foundation for Innovation to build the Alberta Diabetes Research Centre (ADRC).

"It will be a state-of-the-art facility focused on trying to cure this disease," says Dr. Ray Rajotte, project leader for the ADRC. "We already have outstanding diabetes researchers across campus, from nutritionists to molecular biologists, and the new institute will attract even more talent."

In November 2001, the Edmonton team also received CAD$23.7 million (over five years) from the U.S. Juvenile Diabetes Research Foundation—one of the largest grants ever awarded by the foundation. The funds will be directed toward establishing a new clinical centre and advancing islet transplantation research.



TOP: *(SEM) Scanning Electron Micrograph of human islet.*

BOTTOM: *Encapsulated dog islet—capsule open to see islet inside.*

solution. In 1990, he convinced Jonathan Lakey, a graduate zoology student, to do a Ph.D. on improving the isolation of islets from the pancreas to support transplants.

Their work progressed, but like other islet transplant teams, their clinical success was minimal. Transplanted islets simply didn't survive in the recipient's body—most likely because of the anti-rejection drugs used. By the late 1990s, about 450 islet transplant procedures had been attempted worldwide; fewer than 40 patients showed islet function one year after surgery.

In 1993, British surgeon Dr. James Shapiro relocated to Edmonton to do a transplantation fellowship with Dr. Norman Kneteman. Drs. Rajotte and Kneteman soon realized they had found the right man to lead the clinical team as it moved forward with a refined protocol now known as the 'Edmonton Protocol'.

"Islets are quite remarkable," says Dr. Shapiro, Director of the Clinical Islet Transplant Program. "Each one is made up of more than 2,000 cells. They look like tiny snowflakes, smaller than a pinhead, but those cells contain the entire endocrine orchestra. They perfectly control insulin release."

The Edmonton team tried again—this time using fresher islets and more of them. In fact, the team requires two donor pancreases to harvest enough cells for a single transplant. The team also chose to work with healthier patients, bypassing individuals who had already undergone kidney transplants because it was evident that anti-rejection steroids compromised the incoming islets. Finally, the team tried out a new immunosuppressant drug to protect the foreign islets from the patient's immune system.

"The results have been fantastic," says Dr. Rajotte. "The problem is we can't do enough transplants. In Canada, there are only 400 donor pancreases available, but 6,000 new Type I diabetics per year. At best, we can perform transplants on 10 per cent of diabetic patients."

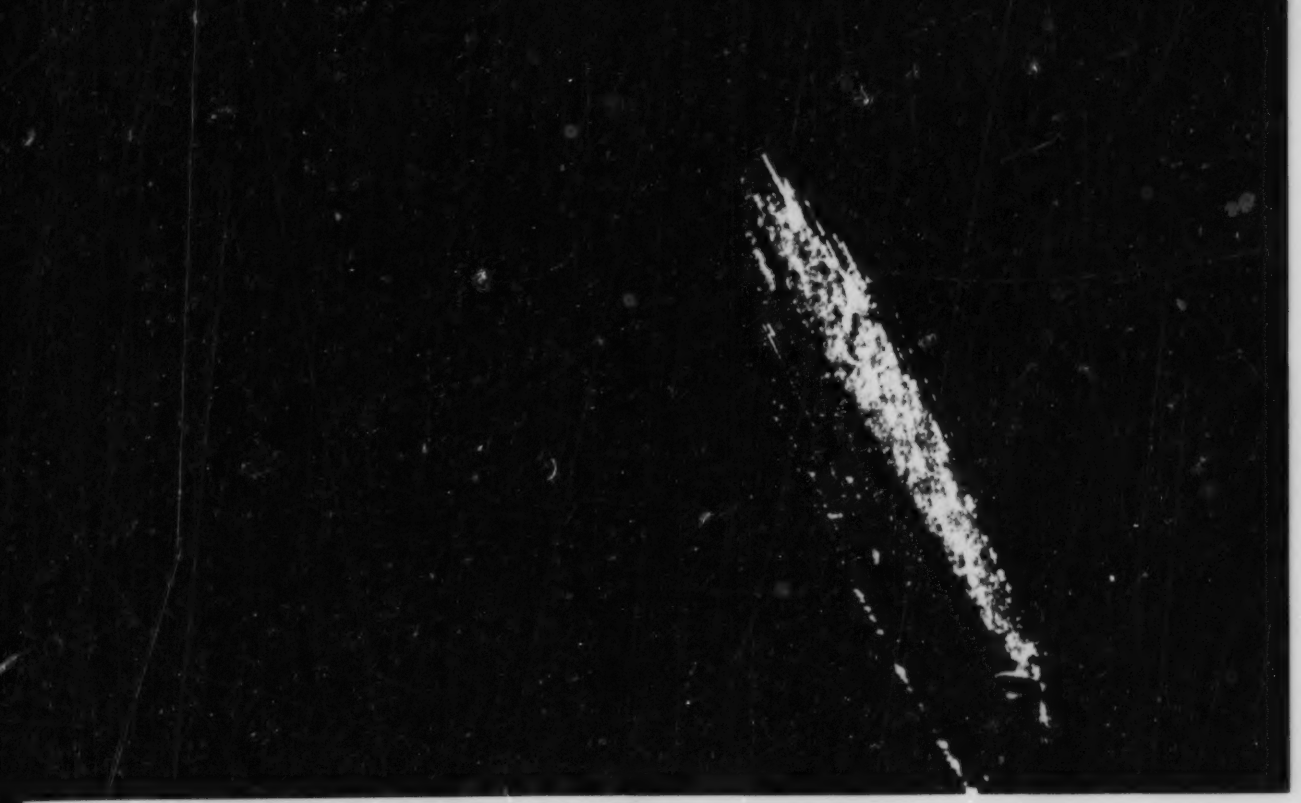
The team has identified two final hurdles to overcome before islet transplantation becomes a widespread treatment option. Once again, they are on the hunt for additional expertise and looking to the biotechnology community for input.

"First, there will never be enough human pancreases to treat all diabetics, so we need to develop alternate sources of islet tissue," says Dr. Rajotte. Dr. Greg Korbutt at the University of Alberta has shown that neonatal pig islets can be isolated, and the Edmonton team is exploring the possibility of using human stem cells to grow new islets in culture.

Second, patients who receive islet transplants must go on a lifelong regimen of immunosuppressant drugs. Dr. Rajotte hopes biotech companies will be able to develop drugs that induce tolerance or find new methods to protect transplanted islets so no drugs are needed.

Riding the wave of attention generated by their success, the Protocol team is ready to expand by establishing the Alberta Diabetes Research Centre and recruiting new staff. The researcher collaborators believe they have every reason to anticipate future triumphs.

"We put the jigsaw pieces together because the right people were around at the right time in the right environment," says Dr. Shapiro. "Canadian scientists have shown they can really excel and lead the field when that happens."



ABOVE: *Isolated human islets—tip of 20-gauge needle for reference.*

LIVING PROOF OF THE EDMONTON PROTOCOL'S EFFICACY

Since being diagnosed with diabetes in his early teens, Edmonton lawyer Bob Teskey estimates that he has stuck a hypodermic needle into his arm more than 40,000 times. He has also monitored his diet with the utmost care.

But his low blood sugar episodes became more erratic—and more dangerous. After blacking out in several boardroom meetings, he adopted a policy of always eating a large meal before driving. Sometimes he awoke in the middle of the night, surrounded by the paramedics his wife had summoned when she found him unconscious in bed.

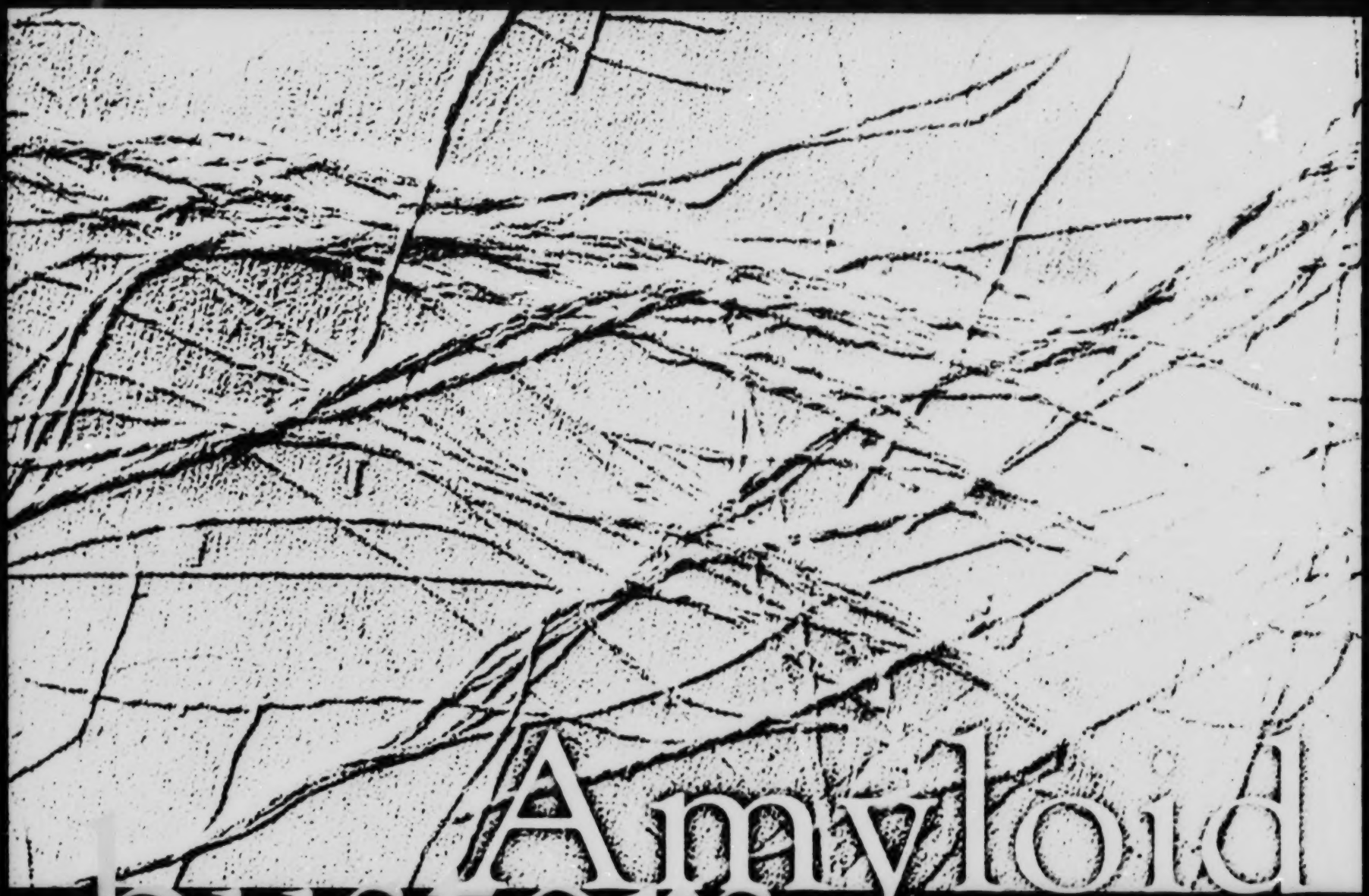
By 1999, conventional therapies ceased to offer any hope, and Teskey resigned himself to an increasingly rapid decline. Then he agreed to try the Edmonton Protocol.

"The effect has been dramatic," says Teskey. "For all intents and purposes, I now function as a normal, non-diabetic. I don't have to worry about the highs and lows, about when or whether I eat. I can do pretty much as I wish."

His needles stowed for almost three years, Teskey now sleeps without fear. Of the 31 transplant patients in Edmonton, 80 per cent remain off insulin after a year. Other researchers have copied the Protocol and achieved similar success.

We are very fortunate to have world-class researchers, people who were attracted to Alberta by stable research funding and the quality of the university and the research establishment. Researchers who set themselves apart from others because they have that spark of creativity.

BOB TESKEY,
ISLET TRANSPLANT RECIPIENT



Amyloid busters

COMBAT DEGENERATIVE BRAIN DISEASES

ABOVE: *Electron micrograph of fibrillar human amyloid protein. In the case of Alzheimer's disease, amyloid fibrils are toxic to surrounding cells, which contributes to severe neurodegeneration.*

A MONTRÉAL BIOTECH FIRM IS WINNING CONVERTS WITH ITS APPROACH TO TREATING ALZHEIMER'S, WHICH SUGGESTS THAT AMYLOID FIBRILS ARE THE ROOT—NOT THE RESULT—OF THIS DISEASE.

Twice in recent months, Montréal-based Neurochem Inc. has attracted widespread attention for its groundbreaking work on degenerative illnesses.

In April 2002, the business magazine, *Forbes*, singled out the biotech company in an article on potential treatments for Alzheimer's disease. Then Neurochem was invited to present at the prestigious International Geneva/Springfield Symposium on Advances in Alzheimer's Therapy.

"There was a small company from Canada at centre stage," says Neurochem President and CEO Dr. Louis R. Lamontagne. "Alzheimer's disease is in need of a treatment with great potential. We had very positive results to report."

In the early 1990s, three professors at Queen's University in Kingston launched a biotech company based on the then radical idea that amyloid fibrils—clusters of deformed proteins that accumulate in diseased brains—are the culprit behind several major diseases that afflict the central nervous system and other organs.

Today, as this theory gains wider acceptance, the firm they created is considered one of the front-runners for an early treatment for Alzheimer's and other degenerative diseases, such as Type II diabetes. It is well documented that up to 170 million people in the world may suffer from some sort of amyloid-related illness.

"When I was trying to convince financiers of the importance of amyloid to Alzheimer's disease, I had a lot more disbelievers than believers," says Dr. Louis Lamontagne, President and CEO of Neurochem Inc. "Now that perception has been reversed."

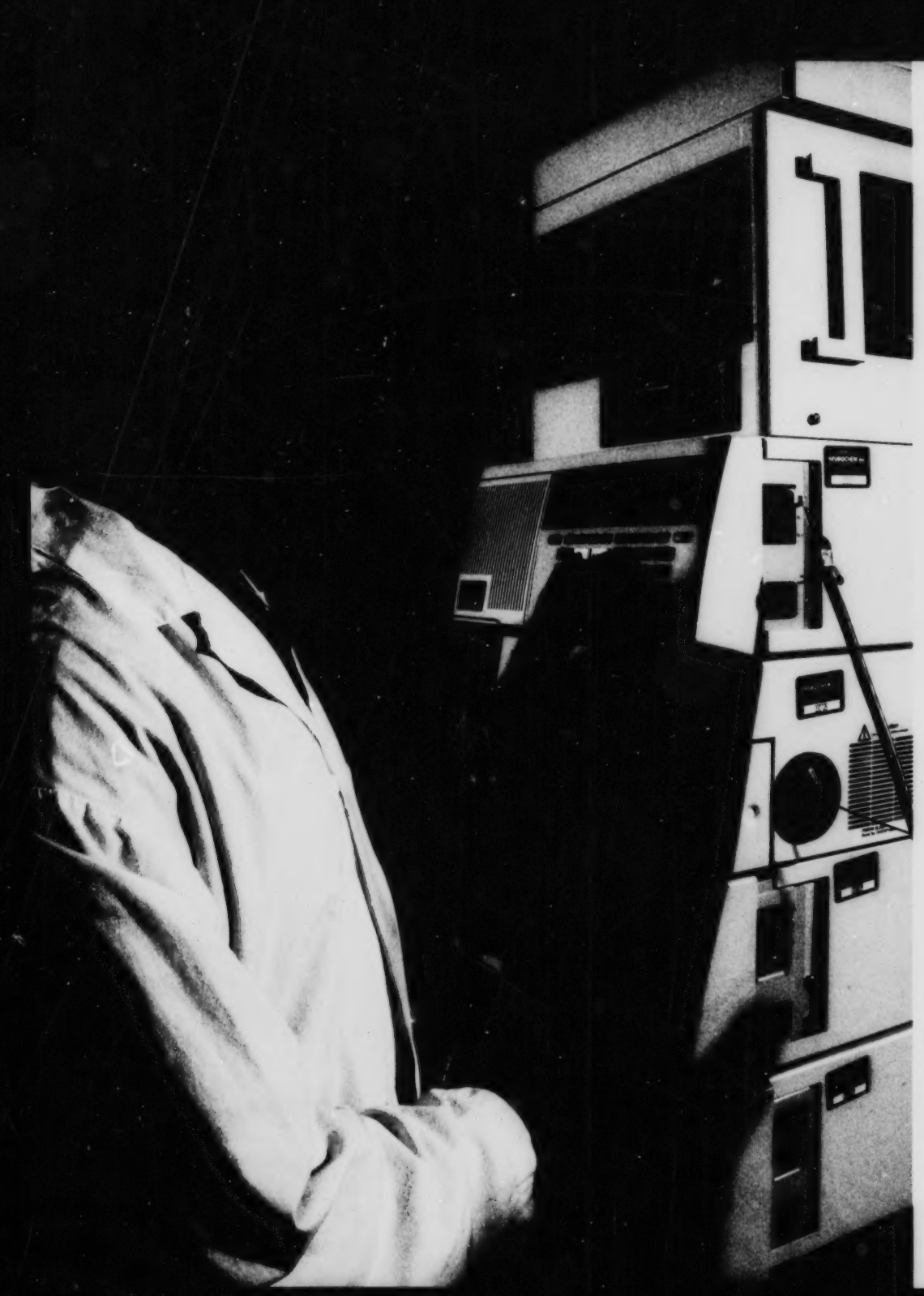
With a handful of promising drug candidates already in clinical trials for diseases such as Alzheimer's, hemorrhagic stroke and secondary amyloidosis, the Montréal-based biotech company appears to be on the brink of commercial success.

Neurochem's strategy is based on the rational design and synthesis of small organic molecules that inhibit the formation, deposition and toxicity of amyloid fibrils.

THE IMPACT OF ALZHEIMER'S

More than 364,000 Canadians—one in 13 over age 65—now suffer from Alzheimer's disease or a related dementia, resulting in a total annual health care cost of CAD$5.5 billion.

In the United States, Alzheimer's and related diseases affect about 4 million people today, with the number of patients expected to rise to 14 million by 2025. Alzheimer's disease is already the third most expensive disease in the United States, and the direct and indirect costs could escalate to more than US$100 billion by 2025.

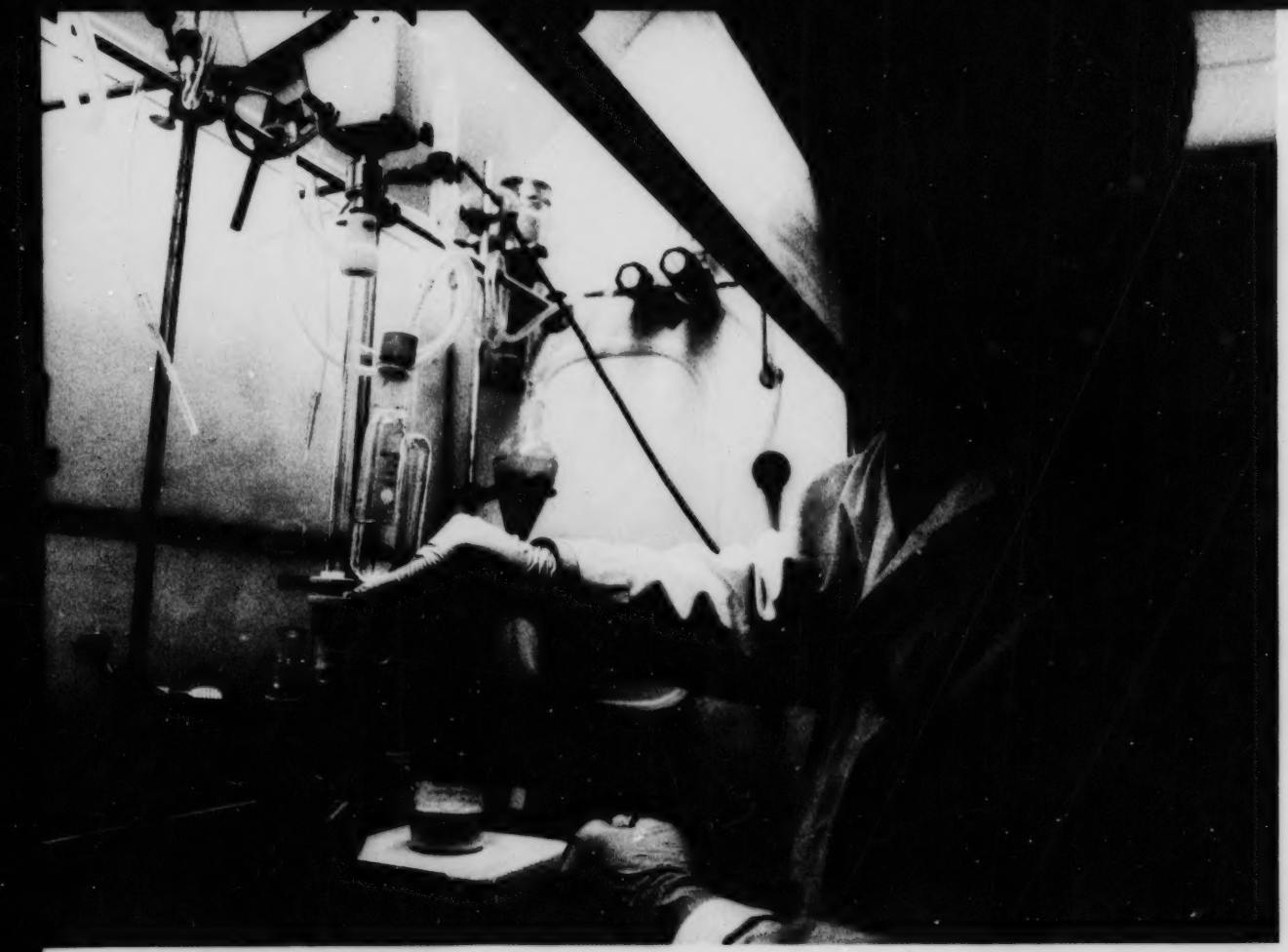


Amyloid fibrils result from the buildup of proteins that normally occur in the body in a benign, soluble form, but which are transformed in the disease process into an insoluble toxic form. In Alzheimer's, the accumulation of these deformed proteins poisons brain cells and prevents associated brain pathways from functioning properly.

DR. FRANCINE GERVAIS,
VICE-PRESIDENT, RESEARCH AND DEVELOPMENT,
NEUROCHEM INC.

Neurochem's drug candidates specifically target sugar-like structures called glycosaminoglycans (GAGs), which play a role in converting amyloid protein fragments into destructive fibrils. By blocking GAGs, the firm's synthetic molecules may prevent fibril formation.

In December 2000, Neurochem researchers demonstrated that Alzhemed™—a therapeutic



candidate for treating Alzheimer's—effectively reduces the advance of the disease in genetically engineered mice. Alzhemed is currently advancing to a Phase II human clinical trial, and Neurochem also has an antigen-based vaccine against Alzheimer's in the works.

Dr. Lamontagne believes that Neurochem is only about five years away from making a significant impact in the fight against Alzheimer's—a sentiment shared by many investors. The company raised more than CAD$36 million in June 2000 when it listed on the Toronto Stock Exchange under the symbol NRM.

Neurochem now employs more than 70 people in research and management. According to Dr. Lamontagne, the company received considerable help in its early years, including strong academic support and government financial assistance in the form of research contributions and R&D tax credits. "Scientifically, Canada is a strong country—better than most," he adds. "There's a tremendous amount of scientific know-how and brainpower here."

FIBRILLEX™ OFFERS HOPE FOR TREATING SECONDARY AMYLOIDOSIS

By 2005, Neurochem Inc. expects to market its drug Fibrillex™ for secondary amyloidosis—a fatal disease for which no treatment is currently available.

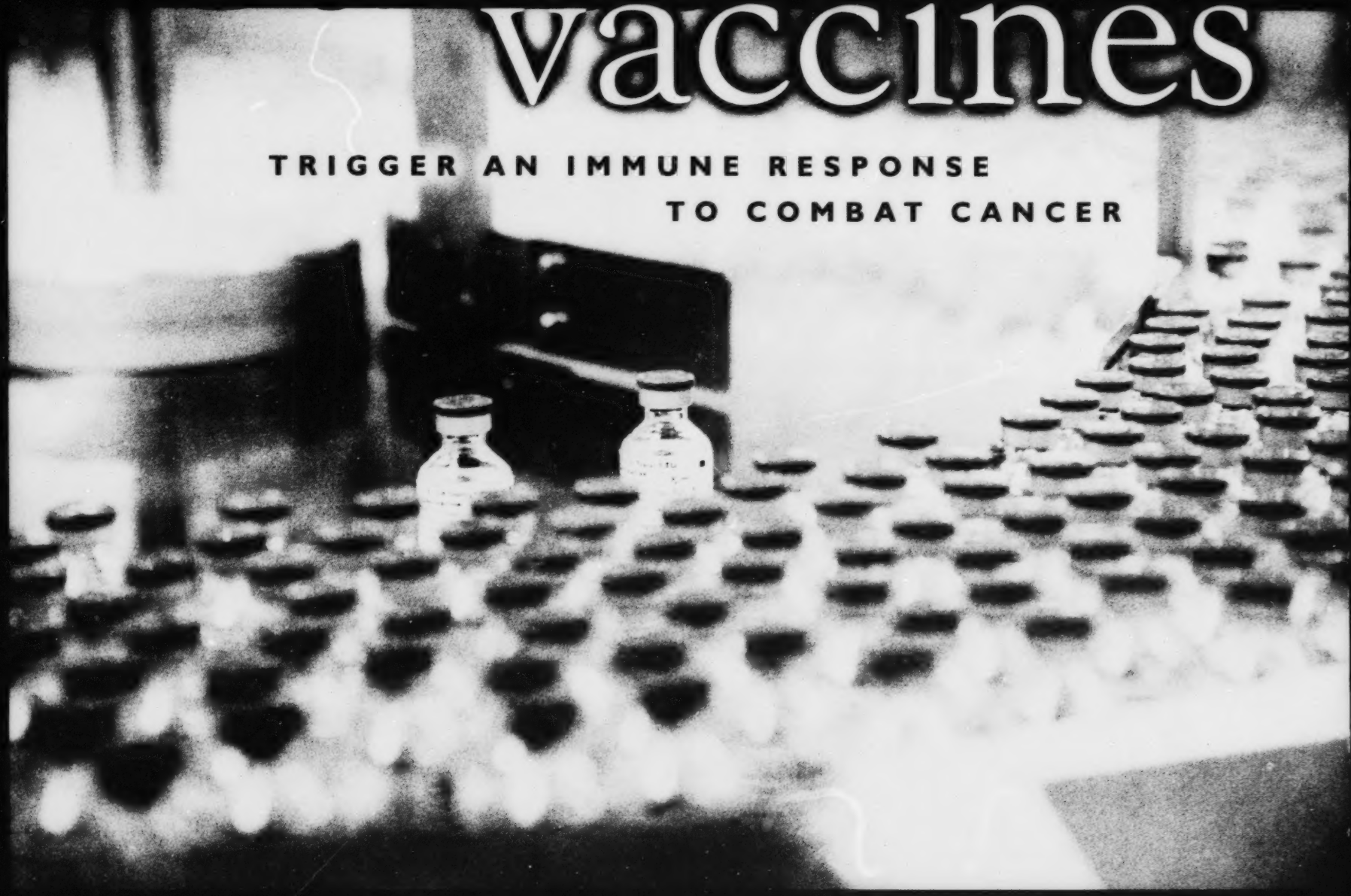
Secondary amyloidosis involves the toxic buildup of amyloid fibrils in the kidneys, spleen, liver and adrenal glands. More than 500,000 patients in industrialized countries are believed to suffer from this disease.

Neurochem's Phase I drug trials, involving laboratory animals, proved so successful that the U.S. Food and Drug Administration agreed to speed up the drug development process by granting Fibrillex pivotal Phase II and Phase III status and combining the two steps.

In addition, Fibrillex has been designated an 'orphan drug' in the United States and Europe. Neurochem thereby benefits from the long market exclusivity and other incentives offered to the makers of drugs developed to treat relatively rare diseases.

vaccines

TRIGGER AN IMMUNE RESPONSE
TO COMBAT CANCER



AVENTIS PASTEUR LTD. IS LEADING A GLOBAL INITIATIVE THAT COULD CHANGE THE WAY WE TARGET CANCER.

In the battle against cancer, the future could rest with a tiny virus.

The canarypox virus ordinarily infects and grows in canaries only, but Aventis Pasteur is harnessing it in experimental vaccines designed to help the human immune system fight back and win against cancer.

These therapeutic vaccines—intended to treat cancer rather than prevent it—may soon join the arsenal of weapons used to control the recurrence of cancer, enhance quality of life, and offer new hope.

As a supplement to traditional treatments, such as surgery or chemotherapy, therapeutic vaccines show great promise in boosting the immune system.

Frustration with the lack of improvement in survival rates in certain cancers led Dr. Neil Berinstein to seek more innovative approaches to the foe with many faces. While training as a medical oncologist two decades ago at the University of Toronto, Aventis Pasteur Ltd.'s program director for cancer became fascinated by the potential of the human immune system to battle disease.

As head of the Aventis Pasteur global Cancer Vaccine Program, Dr. Berinstein now oversees a collaboration involving Aventis Pasteur and top cancer researchers in Canada and around the world, which aims to harness the immune system against cancer.

The program began in June 1997 when Aventis Pasteur announced it would spend up to CAD$350 million over 10 years to develop therapeutic vaccines for cancer. Already, Aventis Pasteur has shown great success in establishing the new concept of therapeutic vaccines as a viable approach to cancer treatment. The program is currently focusing on two main targets—melanoma and colorectal cancer—with further research underway on breast cancer. In North America and Europe, about 50,000 new cases of melanoma and 300,000 new cases of colorectal cancer are diagnosed each year.

"The science has evolved to the point where this is really possible," says Dr. Berinstein. "The idea of a therapeutic cancer vaccine isn't just a dream; it finally is something that is potentially within our grasp."

A PROUD HISTORY OF INNOVATION

When Dr. John G. Fitzgerald founded Connaught Laboratories in 1914, his first success story was diphtheria antitoxin, formulated in an old stable that is still preserved on Aventis Pasteur Ltd.'s Connaught Campus in Toronto. This was soon followed by insulin, polio vaccine and, more recently, the gold standard in immunization, Pentacel—a combined vaccination against five diseases, which is now given to all Canadian children.

Today the company is part of pharmaceutical giant Aventis SA. With 1,000 employees in Toronto, Aventis Pasteur is Canada's largest vaccine company, manufacturing or distributing 30 vaccines and immunotherapeutic products, which protect against 17 infectious diseases and common illnesses.

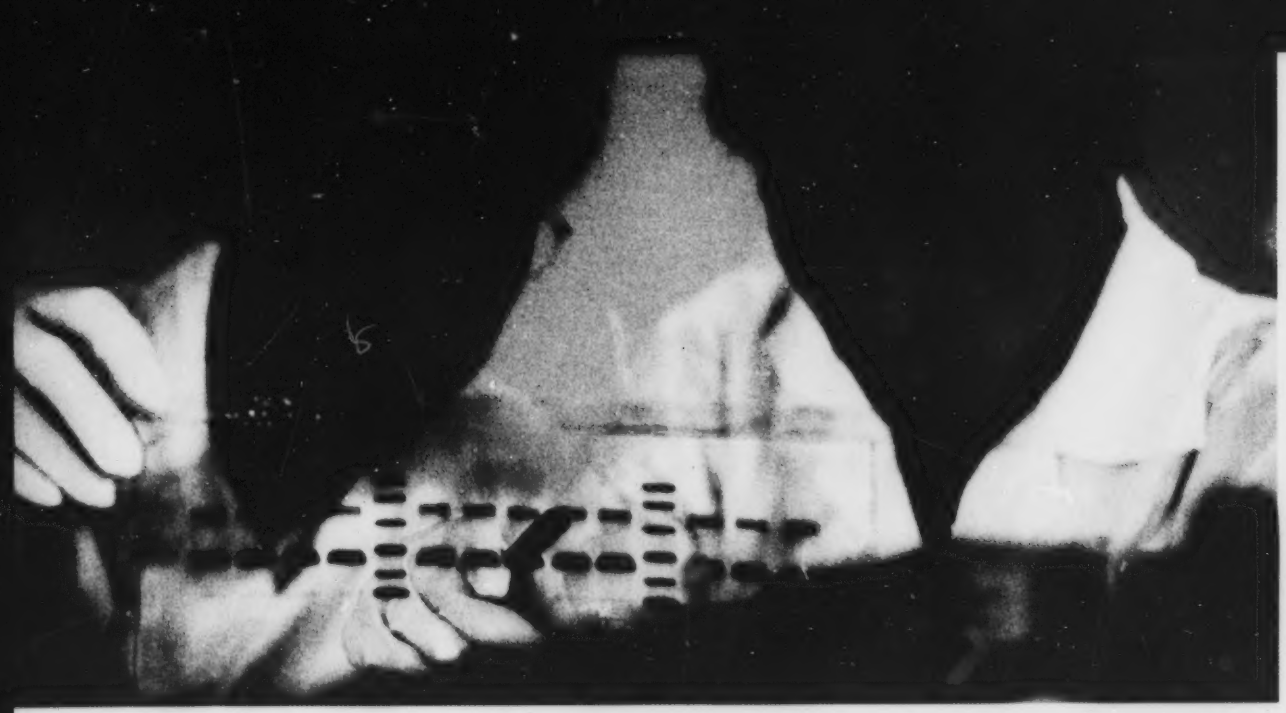
Aventis Pasteur invests almost 40 cents of every sales dollar into research and development in Canada.

In the usual sense, a vaccine prevents disease by preparing the immune system for a possible attack at a later date. Therapeutic cancer vaccines, on the other hand, would be used to 'turn on' the immune system of people who already have the disease and to increase the potential power of current treatments (such as chemotherapy) to fight recurrence.

The research program uses Aventis Pasteur's 'prime-boost' approach to stimulate an immune system attack on tumour cells. "The prime-boost technology first tells the immune system which targets to attack and then revs it up into overdrive for the assault," says Dr. Berinstein. This approach activates both arms of the immune system—the cellular arm, which hunts down and kills target cells, and the humoral arm, which produces antibodies. Both arms must be active for an immune response to succeed against an attacker.

"Unlike conventional vaccines, which turn on the immune system to prevent disease, our vaccines will, it is hoped, stimulate an immune response against a cancer that has already started," says Dr. Berinstein. "We are confident that, in combination with other therapies, this will improve the chances of beating the disease."

Aventis Pasteur has already had an opportunity to test its theories. In 1999, clinical trials of its vaccine against melanoma began at Sunnybrook and Women's College Health Sciences Centre and Cancer Care Ontario/Toronto-Sunnybrook Regional



Cancer Centre. It is here, on two floors of a research building, that Aventis Pasteur runs its global cancer vaccine program. Clinical trial locations have since expanded to include sites in Ottawa and Montréal.

Meanwhile, select cancer treatment centres in the United States are involved in two multi-centre clinical trials with an Aventis Pasteur candidate vaccine for colorectal cancer, one of the most common forms of cancer. In Canada alone, colorectal cancer is the fourth most common type of cancer and the second most fatal form of the disease. Approximately 17,200 Canadians are diagnosed with colon cancer every year, and about 6,400 people die from it. Despite many advances in cancer research, the overall survival rate of patients with colorectal cancers—especially of the bowel—has improved little in recent years. Initial studies will examine the safety of the vaccine when administered with chemotherapy.

Canada is an ideal environment for innovation. This country offers a critical mass of world-class talent working at internationally recognized research institutes.

MARK LIEVONEN,
PRESIDENT, AVENTIS PASTEUR LTD.

Aventis Pasteur is already exploring other cancers that might benefit from the vaccine approach to treatment. "That doesn't mean there isn't a lot of hard work ahead and there won't be some setbacks, but conceptually this is possible now, and I don't think it was 10 years ago," says Dr. Berinstein.

CANADA'S FUTURE LOOKS BRIGHT FOR CANCER VACCINE DEVELOPMENT

As a renowned vaccine leader, Aventis Pasteur Ltd. is set to put Canada on the global map with its research into therapeutic cancer vaccines.

Aventis Pasteur is building a state-of-the-art, high-technology facility dedicated to its cancer vaccine program. The $19-million centre on the company's Toronto campus will house researchers, cancer experts and vaccine technicians, as well as Canada's first robotic arm for the explicit use of vaccine production.

"The new facility is the result of recognizing that therapeutic cancer vaccines require a serious research and development commitment," says Mr. Lievonen.

"Researchers and technicians located there will focus on the development and clinical manufacture of these vaccines, which promise enormous benefits for Canada and the world."

Cellular self-destruction

GENERATES NEW POSSIBILITIES
IN CANCER RESEARCH

WITH A TARGETED APPROACH AND SUBSTANTIAL BACKING, DR. TAK W. MAK PROPELS HIS UNIVERSITY OF TORONTO LAB TO THE FOREFRONT OF CANCER RESEARCH.

Apoptosis is a highly regulated process of cellular self-destruction that's involved in development, stress, or when a cell encounters conditions that seriously compromise its health. Also known as 'cell suicide', it's one of today's hottest topics in biomedical research.

World-renowned immunologist and molecular biologist Dr. Tak W. Mak is making apoptosis a top priority. His interest is captured by the fact that cancer cells never self-destruct—they just keep dividing, creating tumours and disrupting the life cycle of neighbouring cells.

Dr. Mak believes if researchers can determine why cancer cells are immune to apoptosis, they may be able to find ways to reactivate the process.

Although hundreds of scientists worldwide might point to Dr. Tak W. Mak's 1984 discovery of the T-cell receptor as their source of inspiration, Dr. Mak is quick to attribute the thrust of his recent work on cancer research to the largely unknown work of a Shanghai physician.

By unraveling the mystery of the mechanism that allows virus-fighting white blood cells (T-cells) to recognize and destroy foreign invaders such as bacteria or viruses, Dr. Mak effectively resolved 'The Holy Grail of Immunology'. His 1984 article, published in *Nature*, soon became the primary source for thousands of other papers—including 150 from his own laboratory at the Ontario Cancer Institute and University of Toronto.

In contrast, the Shanghai experiment—which Dr. Mak describes as simply as it was carried out—went virtually unnoticed for several years.

"This doctor in Shanghai recognized the finding that a particularly fatal type of leukemia stopped growing when it was cultured in retinoic acid, a common treatment for acne," says Dr. Mak. "In 1987, he injected it in his patients, and was able to achieve a remission of the disease in almost all the patients, where previously 50 per cent would have died within a year."

In 1993, a group of French scientists noticed the retinoic acid experiment, ran an extensive clinical trial, and confirmed that it actually worked. Now, when this treatment is combined with chemotherapy, 75 per cent of the patients survive and are cured.

RESEARCH ROOTS IN CANADA

"Only in Canada does someone become a national hero for not leaving," says world-renowned University of Toronto biomedical researcher Dr. Tak W. Mak. He's referring to the headlines he made in 1987 when he turned down jobs as Head of Pathology at Yale University and Director of the Howard Hughes Institute.

Happily, he's never regretted the decision. "Toronto is a good place to do science," he says. "It's less of a contact sport here than it is in the United States. Perhaps I don't receive as much funding as I would in the U.S., but that's forced me to be more innovative, to use the money to its best advantage every day."

"I'm not sure I would have been as successful anywhere else."

To say retinoic acid cures this type of leukemia—acute promyelocytic leukemia (APL)—is a gross oversimplification of the many factors involved. But in essence, the treatment makes it impossible for APL cells to acquire the amount of retinoic acid they need to differentiate at a critical stage in their development. They lose the ability to mature and divide to produce more cancer cells. Dr. Mak immediately recognized this as an approach that would turn the world of cancer research upside down, as the drug treatment actually targets the molecular defect that leads to the development of cancer.

"From that moment on, I've been trying 18 hours a day to understand what goes wrong with cancer cells, rather than trying to poison them," says Dr. Mak.

Therein lies the fundamental shift. Traditional cancer treatments focus on using chemotherapy to poison cancer cells and induce cell death (apoptosis). The simultaneous death of healthy cells is considered an unfortunate side effect, justified in part by the thinking that cancer cells divide more rapidly than healthy cells, and therefore self-destruct in greater numbers. In effect, scientists hope that the healthy cells will hold out longer.

Increasingly, Dr. Mak is interested in tailoring treatments to address the underlying genetic defects that lead to various types of cancer. Thus he now uses genetics as his tool to understand biology—although he brings expertise in oncology, immunology, virology, and molecular signaling to every project he undertakes. With two main projects on the go, he has already added two important discoveries to his résumé.

The first breakthrough centres on a tumour-suppressing gene known as PTEN, which is mutated in a vast number of cancers. Dr. Mak and his research team have discovered that the mutation activates another gene called AKT/PKB—an enzyme that accelerates cell growth and creates a resistance to apoptosis. Conversely, when AKT/PKB is blocked, normal apoptosis signaling occurs.

THE $100 MILLION MAN

In 1992, the world's largest independent biotechnology company, California-based Amgen, told Dr. Tak W. Mak it was impressed by his research. But Amgen didn't try to lure Dr. Mak to the United States. It simply indicated a desire to fund his research at the Princess Margaret Hospital's Ontario Cancer Institute.

"After our first meeting, Amgen asked me for a proposal for $100,000 in funding over five years," says Dr. Mak. "That figure increased to $300,000, then $1 million before I'd even submitted the proposal, and it continued from there."

In the end, Amgen believed so strongly in Dr. Mak's work, it offered $100 million in funding from 1993 to 2003, and the Amgen Research Institute at the University of Toronto was born.

Negotiations are currently underway to finalize short-term funding to allow the Institute to become fully integrated within the University of Toronto-affiliated university-health network.

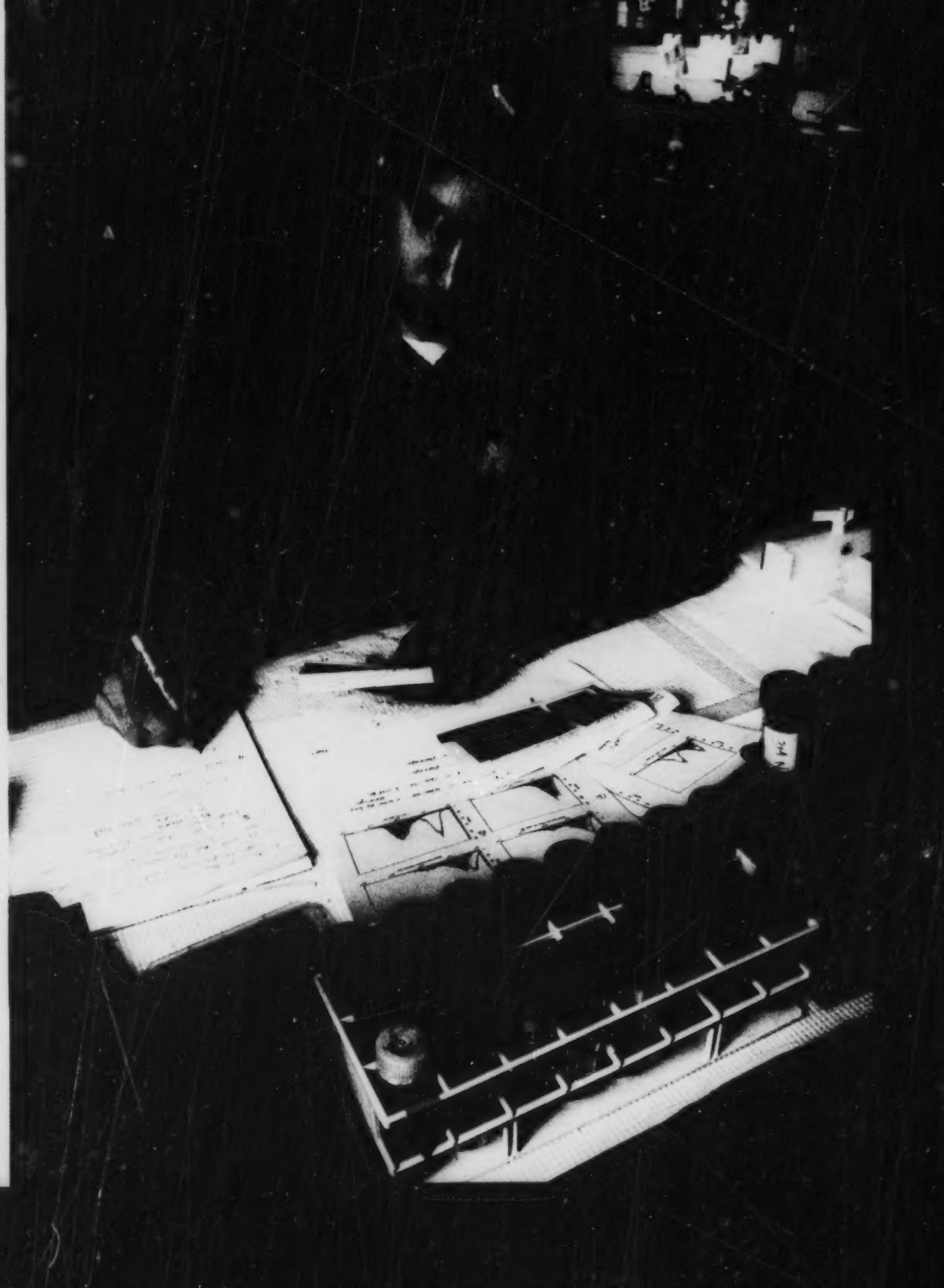
"This makes AKT/PKB a good target for cancer treatment," says Dr. Mak. "In fact, it is perhaps the number one drug target for cancer being pursued by pharmaceutical companies today."

The second discovery concerns Hodgkin's lymphoma. Dr. Mak's team found that when another gene, which codes for the growth factor interleukin13 (IL-13), is expressed in excessive amounts it causes the Hodgkin's lymphoma cancer cells to divide. Once again, they've also proven that when this growth factor is blocked from the cancer cells, apoptosis occurs. And once again, this makes the gene product, IL-13, a good drug target.

In keeping with his reputation for unconventional thinking, Dr. Mak foresees a future in which drug therapy and the immune system team up against cancer. The first step will be to design a more effective way to destroy cancer cells; the second is to involve the immune system in cleaning up the dead cell debris.

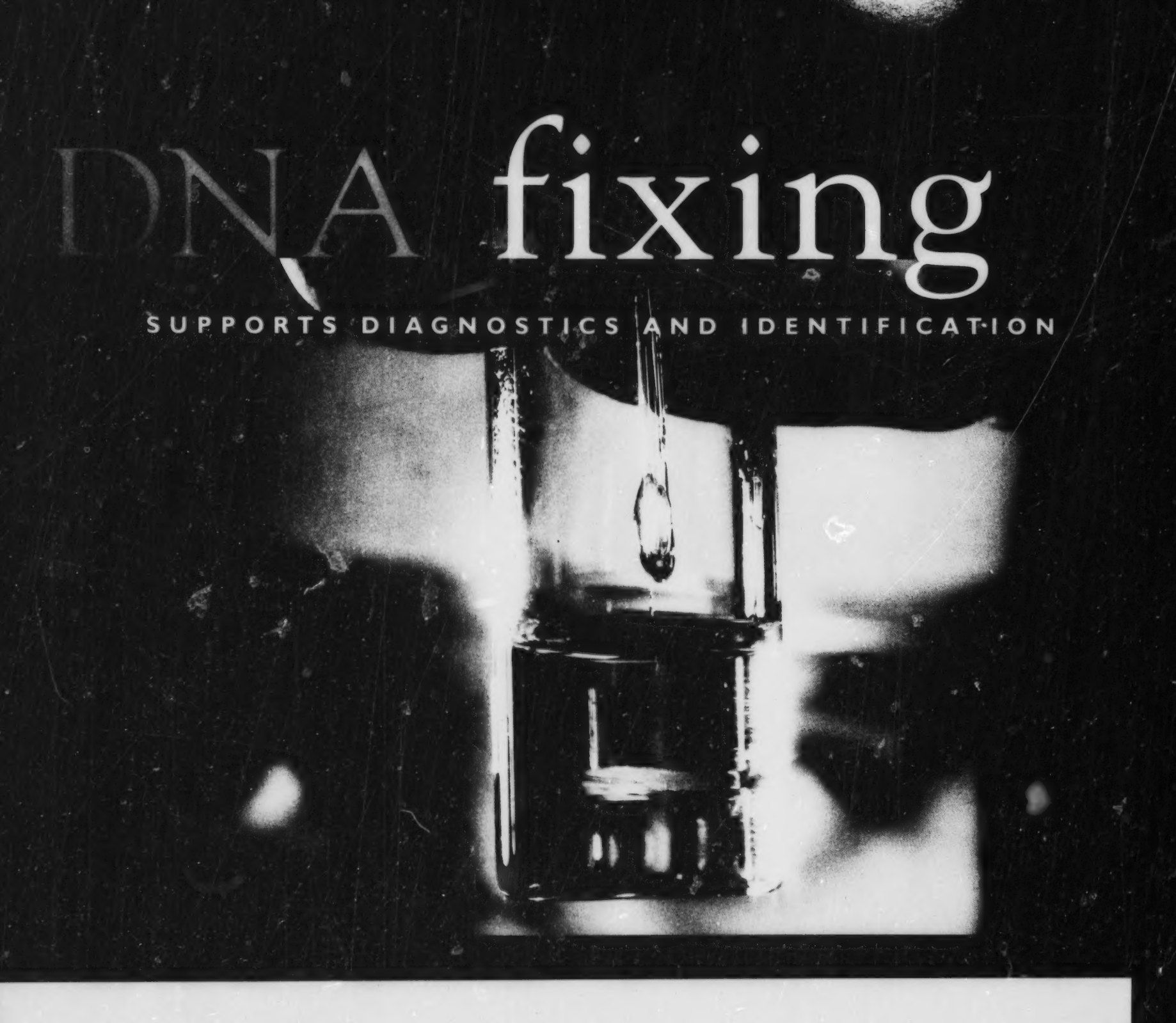
With significant achievements in such a wide range of research, it's no surprise that Dr. Mak is consistently identified as 'a scientist to watch'. In a relatively short time, he's collected an impressive list of accolades, awards and achievements. And with hundreds of researchers the world over assessing the possibility of regulating T-cells to prevent and/or treat AIDS and some forms of cancer, there's a good chance Dr. Mak's humble dreams will be realized in the very near future.

"I can't predict what will happen in the future," says Dr. Mak. "I can only hope that the knowledge we accumulate will lead to new diagnoses and treatments."



DNA fixing

SUPPORTS DIAGNOSTICS AND IDENTIFICATION



DR. CHAIM BIRNBOIM SET OUT TO MAKE IT EASIER FOR PATHOLOGISTS TO COLLECT TISSUE SAMPLES—AND ENDED UP CREATING A DREAM PRODUCT FOR FORENSIC EXPERTS.

DNA samples contain many useful clues for diagnosing disease, but collecting them is both costly and time-consuming. The standard practice is to have a pathologist on duty in the operating room for every biopsy or surgical procedure. To make things even more complicated, preserving samples for later examination requires careful chemical processing and temperature control.

Transfer those strict criteria to the site of a large-scale disaster—an earthquake zone or aircraft crash site—where the goal is to identify victims. It quickly becomes apparent why the inventor of GenoFix™, a method that effectively preserves DNA samples at room temperature, is already getting calls from the international forensic community.

Identifying human remains is an unpleasant but necessary task, wherein a pathological error can lead to further distress in an already devastating situation.

Thus, it's not surprising that Dr. Chaim Birnboim—the scientific mind behind DNA Genotek Inc. and its breakthrough technology, GenoFix™—received a call from the office of New York City's Chief Medical Examiner shortly after the terrorist attack on the World Trade Center. Having read an article about GenoFix authored by Dr. Birnboim and the Royal Canadian Mounted Police (RCMP) in the *Journal of Forensic Sciences*, the medical examiner hoped that it could be a useful asset in the massive job of collecting DNA samples from the disaster site.

Although DNA Genotek was not close enough to commercializing its product in September 2001 to help at the Manhattan site, this request provides a glimpse into the Ottawa firm's future role at disaster scenes. GenoFix is a patented DNA-fixing solution that makes it possible to preserve DNA samples for more than one year at room temperatures. The product thereby avoids the logistical nightmare of setting up facilities to freeze large numbers of tissue samples—often in difficult locations under difficult circumstances.

Dr. Birnboim, a senior scientist at the Ottawa Regional Cancer Centre, first attracted the scientific community's attention in 1979 with a scientific paper describing an effective plasmid

THE GENESIS OF GENOFIX™

"The problem we had at the Ottawa Regional Cancer Centre was that we needed an easier way to collect DNA samples from patients during colon cancer surgery. But the conventional method of having pathologists present at operations around the clock was too time-consuming and too costly," recalls Dr. Chaim Birnboim, a senior scientist at the Cancer Centre who is also now President and Chief Scientific Officer of DNA Genotek Inc.

"I knew how to preserve DNA, but I didn't know how to preserve tissue so a pathologist could easily examine it under a microscope. That's when I hit upon the idea of an alcohol-based fixation technique that would preserve the DNA as well as preserving the histo-morphology—the shape that allows the pathologist to make a diagnosis."

"What I came up with acts like formaldehyde, but is more reliable and useful for pathologists because it doesn't damage the DNA."

LEFT: *Dr. Chaim Birnboim at his tumour bank. He developed GenoFix™ to provide an alternative method of collecting DNA from colon cancer patients.*

DNA purification process, which has become a standard method used in labs around the world. When he began work on GenoFix in 1993, his main objective was to provide an alternative method of collecting DNA from patients who were undergoing surgery for colon cancer. "It took me about three months to come up with a solution that served pathologists' needs without having people on duty to collect samples around the clock."

Realizing that GenoFix could be invaluable wherever large-scale human disasters occur, Dr. Birnboim partnered with DNA Genotek's Chief Operating Officer Robert Morais and Board Chairman Paul Hindo to forge ahead with a commercialization plan. "Highly skilled and highly priced investigators put so much repetitive effort into collecting quality DNA samples," explains Mr. Morais. "GenoFix should be able to simplify large-scale forensic investigations and make them much more cost-effective."

Canada has so many advantages in terms of lifestyle and scientific support structures. And Canadian government people involved in investment and trade promotion are very generous with their time and suggestions.

ROBERT MORAIS, CHIEF OPERATING OFFICER, DNA GENOTEK INC.

ABOVE: *Mr. Robert Morais (left) and Dr. Chaim Birnboim display a prototype Genofix™ DNA preservation kit.*

The RCMP first became interested in GenoFix when Dr. Birnboim contacted scientists at the National DNA Data Bank following the 1998 crash of Swissair Flight 111 off Peggy's Cove, Nova Scotia. DNA Genotek currently has a memorandum of understanding with Canada's largest police force, under which the RCMP agrees to support and promote the use of GenoFix within the international forensic community.

This collaboration has helped spawn additional product lines: GenoFix-based tools that simplify DNA fingerprinting for forensics and law enforcement, which are now ready for the market. So are products based on DNA Genotek's latest technology, Oragene™, which permits the collection of DNA samples from saliva rather than from blood, the usual source. Oragene could prove particularly useful for law enforcement officials who need to obtain DNA from convicted felons. Collecting DNA from saliva is clearly less invasive—and less open to court challenge—than collecting DNA from blood.

"I know we have the best product, but we have to hurry up the educational process in the forensic community," says Dr. Birnboim. "We don't want it to take ten years before people know we've got a winner here. I'm looking at three years—max."

READY FOR MARKET

Despite its very recent development, GenoFix™ is already attracting considerable interest from angel investors and venture capital firms. DNA Genotek is eager to get its product packaged and into the market.

"With most biotech products, there is a long period of R&D and regulatory approval before investors see cash flow," says Chief Operating Officer Robert Morais. "But we're unique: we already have the product. We just need to package it in user-friendly kits and get on with promotion and distribution."

Why the fast-track opportunity? GenoFix is used on dead tissue, so there's no need for further clinical trials or approval from Health Canada or the U.S. Food and Drug Administration.

Targeting AIDS

AT KEY POINTS IN THE VIRAL LIFE CYCLE

NOT CONTENT TO BASK IN ITS PREVIOUS SUCCESSES, THE McGILL AIDS CENTRE TAKES AIM AT THE ELUSIVE HUMAN IMMUNODEFICIENCY VIRUS, BETTER KNOWN AS HIV.

AIDS—acquired immune deficiency syndrome—is projected to become the world's leading cause of death within the next five years. At present, almost 40 million people worldwide are infected with the human immunodeficiency virus (HIV); an additional 15 million have already died.

New drugs have gone a long way towards helping AIDS patients live longer and more productive lives. But HIV is an elusive foe; the virus mutates constantly, developing resistance to the same drugs that once slowed it down.

Dr. Mark Wainberg—founding director of the McGill AIDS Centre—is searching for new angles of attack against HIV. The question is, how do you hit a moving target?

Since 1996, drug cocktails have transformed the diagnosis of human immunovirus (HIV) from a death sentence into a manageable condition. In industrialized countries where patients have access to combination drug therapy, almost 1.5 million people live with HIV. By effectively staving off full-blown acquired immune deficiency syndrome (AIDS), the therapy has given many AIDS patients a second chance to lead full, productive lives.

Although treatment has come a long way, the virus seems to be always one step ahead. "One of the biggest problems is that HIV is mutating all the time, and so becomes resistant to drugs," says Dr. Mark Wainberg, Director of the McGill AIDS Centre at McGill University (Montréal, Québec). "So we need to find newer drugs, and we need to identify novel targets in the viral life cycle that these drugs can be active against."

Long before AIDS became a household word, Dr. Wainberg was studying how viruses, such as the common cold virus, can temporarily suppress the immune system. "I had always been

AN EARLY BREAKTHROUGH

While working in collaboration with BioChem Pharma Inc., Dr. Mark Wainberg was the first independent researcher to demonstrate the anti-HIV properties of 3TC—one of the key drugs used in the highly successful AIDS combination therapies or 'cocktails'. Like AZT and other AIDS-cocktail drugs, 3TC works by attacking the enzyme that initiates reverse transcription—the conversion of viral RNA into DNA.

Over the past decade, more than a million people have taken 3TC, which is still the leading AIDS drug in worldwide sales. Dr. Wainberg counts the development of 3TC among his proudest achievements. "It's a contribution that has helped save the lives of hundreds of thousands of people throughout the world," he says. "Nothing tops that."

AFRICA AT WAR WITH AIDS

Of the almost 40 million people infected with HIV, about 28 million live in sub-Saharan Africa. "In terms of prevention, we've made progress in North America and Europe, but in the developing world we're absolutely losing the battle," says Dr. Mark Wainberg, director of the McGill AIDS Centre.

The new AIDS drugs that are prolonging lives in North America are largely unavailable in poor African countries. Dr. Wainberg is encouraging governments in developed nations to take an active role in establishing funds that will make these drugs available in developing countries.

fascinated by how these tiny little things could do so much damage," he says.

When the AIDS epidemic broke in the early 1980s, Dr. Wainberg was the first scientist in Canada to isolate the virus—which directly attacks the immune system—and begin research on possible treatments. In fact, his lab was the first in the world to demonstrate the anti-viral properties of the breakthrough AIDS drug called 3TC and among the first groups to identify the problem of HIV drug resistance. For his groundbreaking work, Dr. Wainberg received the Order of Canada—the country's highest honour for lifetime achievement.

With HIV, people are infected for life, and the virus is mutating all the time. That's a pretty lethal combination.

DR. MARK WAINBERG, DIRECTOR, McGILL AIDS CENTRE

Now one of the world's leading AIDS researchers, Dr. Wainberg—who is also Research Director at Montréal's Jewish General Hospital—is looking for new ways to keep HIV in check. One promising new target is TAT, a protein involved at multiple points in the HIV life cycle. TAT enhances the synthesis of viral RNA, and also seems to promote reverse transcription—the process whereby viral RNA is copied into a host cell's DNA and HIV reproduces itself.

"TAT is something that the virus absolutely needs for its replication," says Dr. Wainberg. "If we could come up with drugs that will attack it, then viral replication might come to a standstill."

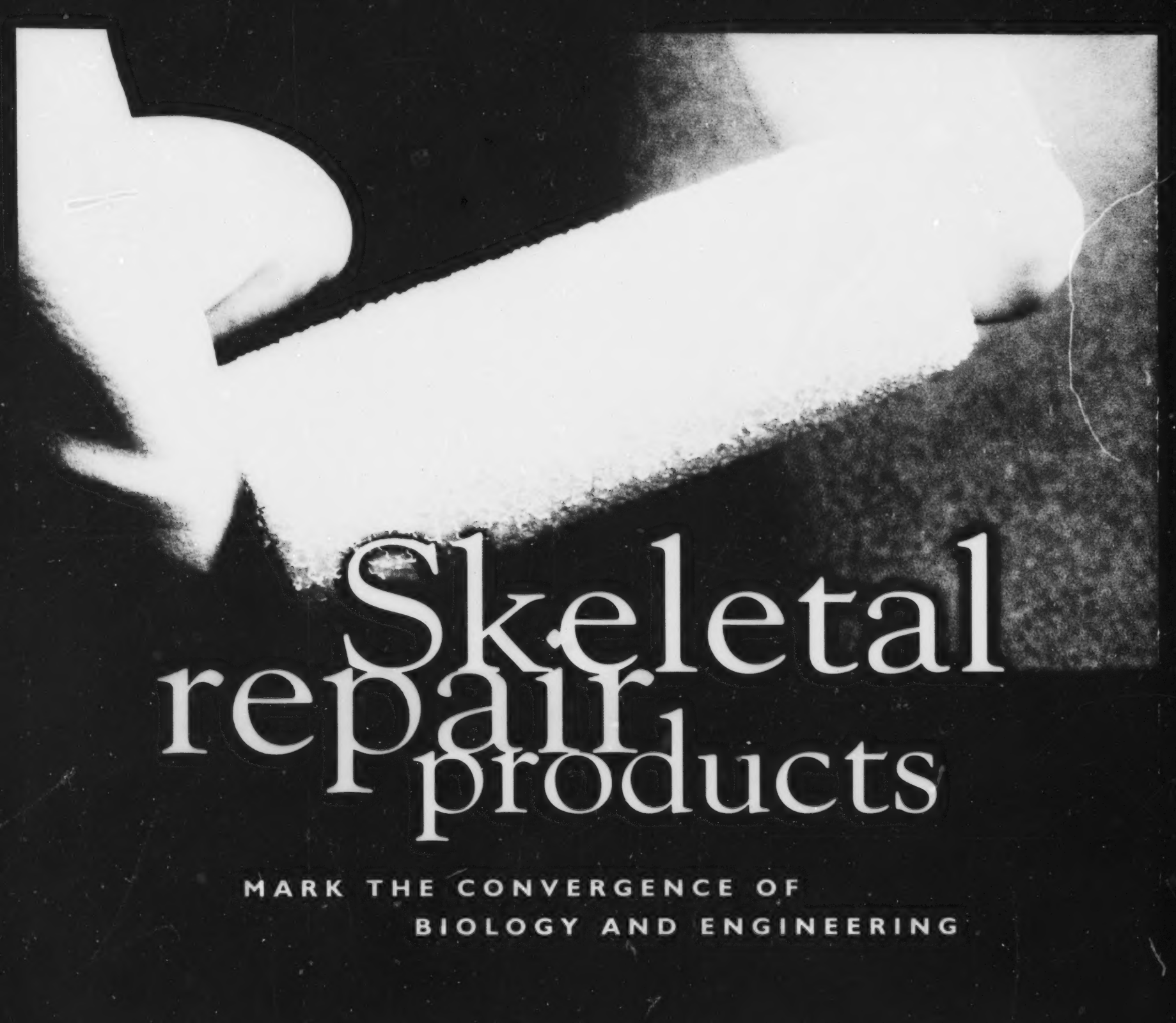
In Dr. Wainberg's lab at the McGill AIDS Centre, researchers are screening tens of thousands of compounds for antiviral activity. They hope to find key ingredients that keep TAT from supporting HIV synthesis and replication. It may be something as straightforward as a compound that blocks TAT from binding to another protein. Or it may involve finding out how several compounds interact.

In one sense, the key is to try everything. "When we get hits, then we keep working to see if this compound could be used as a drug," says Dr. Wainberg.

Although new and improved treatments offer promise for slowing growth of the virus, Dr. Wainberg doesn't think there will be a cure for HIV any time soon. This highlights the need to constantly pursue new drug development, for which Canada offers an ideal environment.

"The Canadian talent pool is second to none, and the costs of doing research and development in Canada are far lower than in the U.S. and Western Europe," he says. "The proof is in the pudding. We've already participated in successful drug development, not just for HIV but for other diseases as well."

In the future, Dr. Wainberg hopes to generate new insights and new drugs that will make a difference for HIV patients. He says that being part of the drug discovery process has been a wonderful experience. "It enables you to feel that you've been part of saving people's lives. I don't know what could be more meaningful."


Skeletal repair products
MARK THE CONVERGENCE OF
BIOLOGY AND ENGINEERING

THROUGH THE LABORATORY PRODUCTION OF 'LIVING' BONE AND CARTILAGE, MILLENIUM BIOLOGIX INC. IS TRANSFORMING ORTHOPAEDICS AND TISSUE ENGINEERING—AND SUPPLYING AN EFFECTIVE TEST BED FOR DRUG DISCOVERY.

In the early 1990s, a graduate student was experimenting on bone cell cultures in Dr. Michael Sayer's physics lab at Queen's University in Kingston, Ontario. A serendipitous mistake led to the discovery of a unique synthetic substance that acts like natural bone mineral—to the point that normal cells accept its implantation without hesitation.

Building on the work of Dr. Sayer's team, Millenium Biologix Inc. was launched in 1993 to develop and market the material, dubbed 'Skelite™', for rapidly growing markets involved in the research, diagnosis and treatment of skeletal diseases. Currently available as both implantable bone grafts and tissue engineering scaffolds, the material is now part of a growing family of innovative products and services. As Millenium earns recognition as a pioneer in the repair and replacement of skeletal tissue, Skelite is receiving invitations to travel into outer space to help NASA study why micro-gravity induces bone density loss.

Almost everyone experiences a loss of bone density and joint degeneration over the course of a lifetime. The combination of an aging population and more physically active lifestyles means there is greater need for therapeutic products to treat degenerative bone diseases such as osteoporosis, and joint diseases such as osteoarthritis.

"The global market for synthetic bone replacement and cartilage tissue products is US$5 to $6 billion," estimates Sydney Pugh, President and CEO of Millenium Biologix Inc. of Kingston, Ontario. "Our primary products— Skelite™, the Osteologic™ research line, and Cartilogic™, a total system for clinical tissue engineering—stimulate natural bioprocesses to safely and reliably produce living tissue, and also support pharmaceutical R&D."

Currently, most skeletal implants are constructed of relatively inert metals. Although such devices may be mechanically strong, they are not biologically active. They generally fail to integrate with natural tissue and ultimately malfunction at the point of connection to the skeleton. Furthermore, although the risk of toxicity or immune system rejection is minimal, metal implants are not truly compatible with human systems.

LIVING BONE IN OUTER SPACE

Astronauts may lose up to 10 per cent of their bone mass during a single month in space. Scientists have yet to determine why this happens or—more importantly—how to minimize the risks associated with longer space missions.

Since the early 1990s, Millenium Biologix Inc. has provided both the proprietary bioactive materials and the integrated OSTEO™ hardware needed for scientists to carry out various studies on bone cell function, growth, and tissue engineering for in-orbit missions. OSTEO has laid the foundations for Millenium's advanced clinical tissue engineering systems, which are now close to commercialization on earth.

The company is currently involved in joint projects with the Canadian Space Agency, the European Space Agency and NASA, including another payload of Skelite™ on the space shuttle Columbia's STS-107 mission in the summer of 2002.

"Skelite is biocompatible so it is not rejected by the body," says Mr. Pugh. "But it is also bioactive, which means that it is naturally reabsorbed and replaced through ongoing bone growth."

Millenium Biologix offers multiple Skelite lines that easily surpass the limitations of current synthetic bone implants. Current products range from powders and granules, which are designed to fill small, irregular bone voids at common fracture sites, to large porous synthetic scaffolds that can repair problems such as badly damaged limbs or collapsing spines.

Skelite's similarity to normal bone spans both its chemical makeup and its detailed physical structure. Following the initial healing phase, the normal cell-mediated remodelling process gradually replaces Skelite devices with natural tissue.

Because it can be manufactured at low cost in various function-specific configurations, Skelite satisfies critical needs in a variety of medical and biotechnology applications. It belongs in a class of materials called bone graft substitutes that's already recognized and well accepted by international regulatory agencies.

In 1996, Millenium Biologix entered into an agreement with Mississauga-based Allelix Biopharmaceuticals Inc. to develop that company's novel extracted bone cell stimulating factor (BCSF), which accelerates natural bone growth. Since Allelix's merger with NPS Pharmaceuticals of Salt Lake City, Utah, a division of Millenium Biologix continues to operate within the NPS Allelix facility in Mississauga.

"Millenium Biologix has taken BCSF and further developed it into a family of synthetic, small molecular weight peptides with demonstrated activity in bone and cartilage," says Mr. Pugh. "These

ABOVE: *The OSTEO-2 (Osteoporosis Experiment in Orbit-2) payload is scheduled for launch on NASA's STS-107 mission in July 2002. Using technology developed by Millenium Biologix, OSTEO-2 aims to better understand bone loss during space flight.*

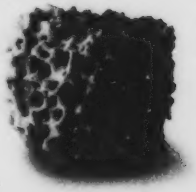
are at various stages of development, and clinical trials are expected to begin in the near future."

In addition, Millenium Biologix has developed the Osteologic line of products for medical and pharmaceutical research, which are marketed worldwide by the New Jersey-based medical technology firm, Becton Dickinson. Osteologic provides a unique bone cell assay technique to measure the effects of new drugs. The technology uses a sub-micron film of synthetic bone in one format, and small three-dimensional macroporous constructs in a second format, which can be exposed to various treatments and then analysed using the Microst Image Analyzer™—produced by Millenium Biologix.

Well-educated and creative people, an appetite for excellence, and a strong competitive spirit propel our drive towards leadership in clinical tissue engineering.

SYDNEY M. PUGH, PRESIDENT AND CEO, MILLENIUM BIOLOGIX INC.

The company's products already generate strong revenues by creating valuable new market opportunities and by offering competitive advantages in existing markets. Millenium Biologix has R&D and production facilities in Canada and Switzerland, as well as an extensive network of international partners.



REDUCING RISK IN BONE REPAIR AND REPLACEMENT

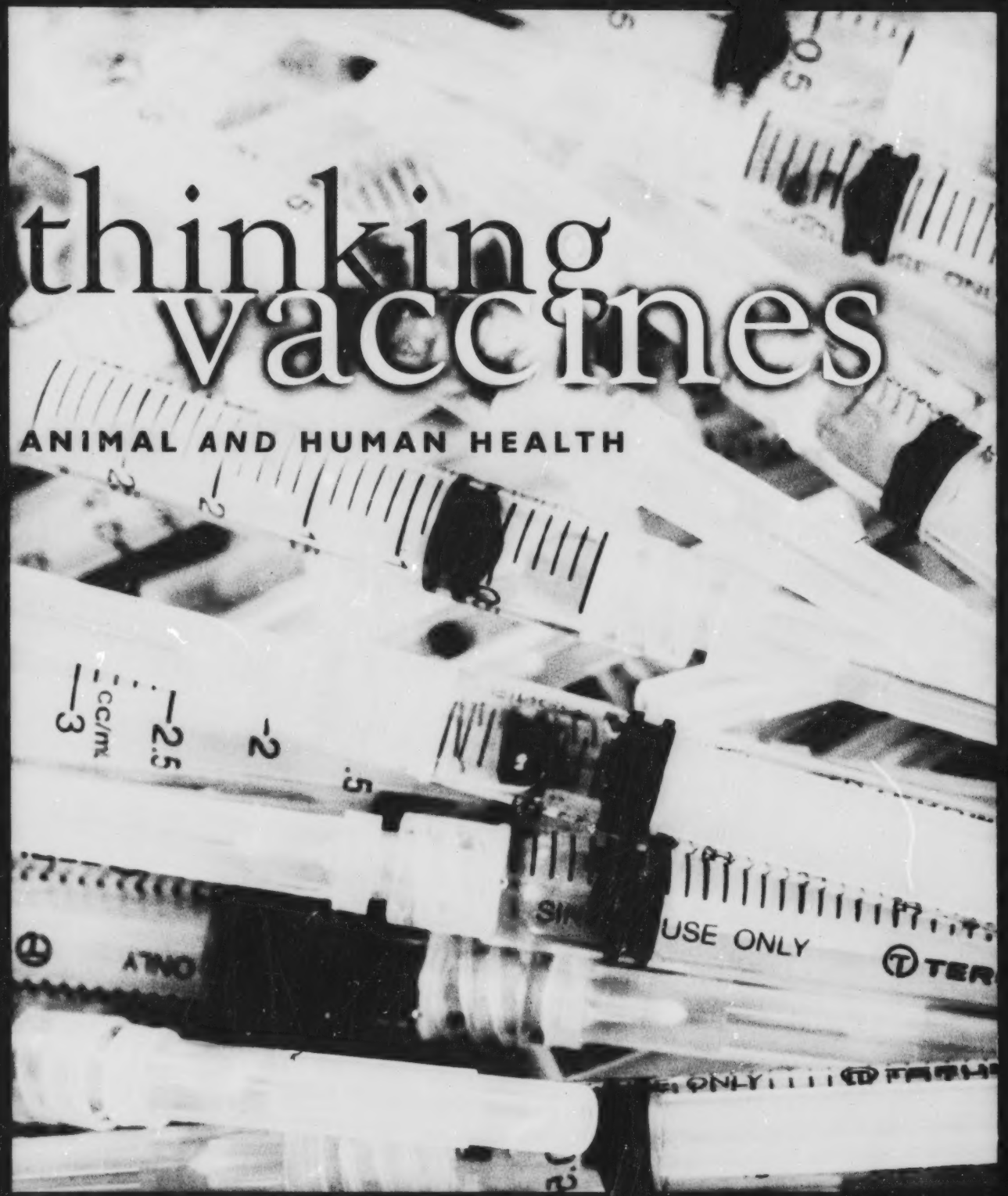
Millenium Biologix Inc. is the world leader in turn-key human autologous tissue engineering—a technique that prevents the rejection of bone implants by eliminating the need to introduce foreign tissue in the patient's body.

Instead, early-stage bone cells are harvested from the patient and seeded onto a synthetic scaffold in a laboratory setting to create a natural mineralized matrix. The result is a 'hybrid bone graft' that can be inserted to repair or replace damaged or diseased bone without the risk of stimulating an immune system attack.

These hybrid grafts can serve as a 'time release' drug delivery system. Millenium Biologix is also exploring the idea that such tissue could be stored in 'bone banks' for broader human use.

thinking vaccines

TO IMPROVE ANIMAL AND HUMAN HEALTH



OVER THE PAST 25 YEARS, VIDO HAS BUILT ITS REPUTATION BY CHALLENGING THE NOTIONS OF WHEN, WHERE, WHY AND HOW VACCINES ARE DELIVERED.

The Veterinary Infectious Disease Organization (VIDO) is a world leader when it comes to pushing the envelope of vaccine development. Expertly bridging the great divide between academia and industry, the Saskatoon-based research institute has recorded a series of impressive firsts: an enteric (intestinal) combination vaccine for cattle, a genetically engineered vaccine for shipping fever, and now an animal vaccine designed to protect humans from a deadly *E. coli* strain.

In the process, VIDO has forced regulators and industry to consider new questions and come up with new answers.

"Our vision is to be doing things today that other people think about doing five years from now," says Dr. Lorne Babiuk, Director of the Veterinary Infectious Disease Organization (VIDO). "We are very opportunistic. We scour the literature. We look at new ideas and concepts, and we capitalize on them."

Dr. Babiuk and his colleagues at VIDO have a long history of exploring new territory. Ever since the creation of VIDO in 1975 by the University of Saskatchewan, this one-of-a-kind research institute has been pushing the limits of what's possible. Consider its impressive track record.

In the early 1980s, VIDO introduced the world's first enteric combination vaccine for cattle—a triple-threat vaccine that controls 'calf scours' or diarrhea by protecting against bovine rotavirus, coronavirus, and *E. coli* K99. VIDO scientists also developed a technique for growing rotavirus, which has been widely adopted by biopharmaceutical firms around the world. Later in the decade, VIDO created the world's first genetically engineered vaccine for any animal species. The pioneering vaccine prevents shipping fever, a disease that costs the North American cattle industry US$0.5 to $1 billion per year.

In the late 1990s, VIDO made its first foray into human health. By collaborating with scientists at the University of British Columbia, scientists developed a cattle vaccine against the *E. coli* 0157:H7 strain. Although this organism is harmless to cattle, it leads to the deadly 'hamburger disease' in humans. The vaccine is currently undergoing field trials.

CONTROLLING FOOD- AND WATER-BORNE PATHOGENS

When the Veterinary Infectious Disease Organization (VIDO) helped develop a successful cattle vaccine against the *E. coli* 0157:H7 pathogen, it presented a unique problem for the Canadian Food Inspection Agency and the U.S. Department of Agriculture.

"One of the main criteria for licensing an animal vaccine is to show that it reduces disease," says Dr. Lorne Babiuk, Director. "The *E. coli* vaccine fails this test because the bacteria doesn't make cows sick."

VIDO explained that using the vaccine reduces the amount of *E. coli* shed by cattle and that lower levels of environmental contamination indirectly reduce the chance of human exposure and disease.

Regulators bought the argument, and VIDO has since launched an ambitious food and water safety program. It is now developing vaccines against the Cryptosporidium parasite, which infects cows and humans, and the *Campylobacter* bacteria, which is spread by chickens.

VIDO recently chalked up another first by successfully vaccinating a fetal lamb against viral infections that often occur during labour and delivery. Some day, this groundbreaking technique may protect human infants against a wide range of potentially fatal diseases that can be passed from mother to child in the birth canal.

"We started out as a veterinary infectious disease organization," says Dr. Babiuk. "As we evolve, we're capitalizing on the convergence of human and animal health. In the future, our acronym will still be VIDO, but we may change our name from the Veterinary Infectious Disease Organization to the Vaccines and Infectious Diseases Organization."

What won't change, however, is its recipe for success. Wholly owned by, and based at, the University of Saskatchewan in Saskatoon, VIDO was one of the first Canadian research institutes created to bridge the divide between academia and industry. Its *raison d'être* is to turn sound research ideas into viable commercial concepts—which then generate economic benefits.

PROTECTING THE FETUS FROM INFECTIOUS DISEASE

Herpes simplex, HIV, group B streptococcus and hepatitis B—just a few of the life-threatening diseases infants can contract in the birth canal or shortly after birth. Every year, millions of infants worldwide die of such infections before age one. Consider the case of genital herpes.

"If the child is born through the birth canal to a mother who has active genital herpes, there's a 90 per cent chance that the child will get infected," says Dr. Lorne Babiuk. "And there's about a 90 per cent chance that it will die or have very serious long-term consequences."

VIDO's pioneering method for vaccinating the fetus could eliminate the current practice of delivering at-risk babies by Cesarean section and protect against infections that occur when the mother's water breaks early and viruses swim up the birth canal.

One of VIDO's current preoccupations may seem well beyond the mandate of an animal health research institute, but it is bound to be of huge interest to both pharmaceutical companies and health care providers—across many species.

"All of our children's vaccines today are given with needles. This can be very unpleasant for both the children and their parents," Dr. Babiuk deadpans. "We're looking into needle-free delivery of vaccines for both humans and animals. We're developing a family of vaccines, some of which can be delivered through the skin, intra-nasally, or orally, using little tablets."

VIDO's ability to pursue such a breadth of research reflects its unique structure. Although not a legal entity, VIDO operates at arm's length from the University of Saskatchewan. The university has the final say on major decisions, but VIDO generates revenue and has a board of directors. Unlike most academic research units, it retains total control over its intellectual property and keeps all the royalties.

In fact, VIDO holds more patents (42 at last count, with another 20 pending) and earns more royalties than the entire university. All of its private-sector revenues—approximately CAD$2 to $3 million per year—support further research. VIDO also receives funding from provincial, national and international sources, as well as the livestock industry.

The formula is definitely working. VIDO is planning a massive expansion that will see its current staff of 85 increase to more than 140 people within the next two years. When complete, VIDO may rank as the world's largest "discovery team" in veterinary medicine and infectious diseases.

"Large biopharmaceutical companies don't do much 'discovery' work. They focus on development work. We don't do much development work, so we partner with companies to bring our discoveries to commercial realization," Dr. Babiuk concludes.

In 1984, Dr. Lorne Babiuk was awarded the first Industrial Research Chair in Biotechnology, sponsored by the Natural Sciences and Engineering Research Council of Canada. Dr. Babiuk held the research Chair for more than 10 years.

cell
REWRITES NATURE'S SOFTWARE

DR. MARC-ANDRÉ SIRARD SEEKS THE GENETIC CODE THAT CAN ERASE A CELL'S HISTORY AND REPROGRAM ITS DESTINY.

The oocyte—an unfertilized egg cell—is the only cell in the body that does not age or die, remaining frozen in time until a sperm triggers its transformation into an embryo.

Oocytes also have the unique capacity to turn back time in other cells. Dolly the sheep—the cloning project of scientists in Edinburgh, Scotland—is the product of fusing a mammary cell from one adult ewe and an oocyte from another. The oocyte reversed the mammary cell to time zero: the starting point of a new individual.

No one knows how the oocytes do it, but one thing is certain: it's all in the genes.

Unlocking the secret of the oocyte's immortality could lead to new treatments for human diseases—from Parkinson's to diabetes to cancer.

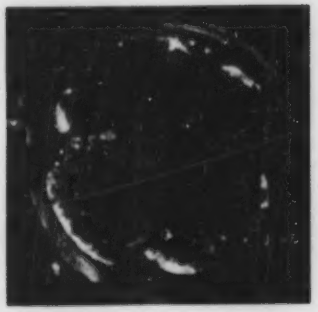
In the world of cells, the oocyte is huge. A full 100 microns in diameter, or about the size of the smallest speck of sand visible to the naked eye, it is the largest cell in the human body. Within that speck rests the power to decide when life begins, to make old cells new again, or to erase a cell's memory and program it for a new role.

Dr. Marc-André Sirard has spent more than 20 years studying the oocyte, which he calls "a wonderful and immortal cell." His research has answered questions about why some oocytes become embryos, while others don't. Thanks to this groundbreaking research, Canada is now a leader in bovine genetics.

But for Dr. Sirard, the real treasure is hidden in the genes: somewhere in the oocyte's DNA is the genetic coding that tells a cell how to stay young, or reverses an adult cell back to the embryo stage. That genetic code could bring radical new treatments for a wide range of human diseases.

During a 10-year research partnership between Semex Alliance and Laval University (Québec City, Québec), where he directs the Research Centre in Reproductive Biology, Dr. Sirard focused on increasing egg quality in livestock. He found that the hormones administered to cows during *in vitro* fertilization caused rapid growth of the follicles—the small balloons in which oocytes grow.

ABOVE: *Human embryo one day after fertilization*



ABOVE: *Bovine embryo two days after fertilization*

ABOVE: *Porcine embryo six days after fertilization*

However, the follicles grew so quickly that the developing oocytes could not keep up. The result: a windfall of oocytes, but many too weak to survive.

By modifying the homones to create a 'plateau', or resting phase, for the follicles, Dr. Sirard was able to increase the number of successful embryos from 35 to 85 per cent, a success rate achieved nowhere else in the world.

"It's not because we found a magic bullet," he says. "It's because we took the time to understand how the ovary works, and how it influences the oocyte to become an embryo."

I want to understand this system, built in by nature, that makes us age, while the oocyte does not.

DR. MARC-ANDRÉ SIRARD, DIRECTOR, RESEARCH CENTRE IN REPRODUCTIVE BIOLOGY, LAVAL UNIVERSITY

Companies around the world now use Dr. Sirard's procedure to breed better animals more quickly. Researchers on human fertility are also taking notice. "They're looking at the work we've done in animals, and they're realizing that maybe they also need to allow time for the follicles to differentiate, and produce better oocytes, not just more of them," he says.

With a solid understanding of what oocytes do, Dr. Sirard now wants to know how they do it. The oocyte is the only cell that can reverse the natural process of differentiation, whereby generic embryonic cells become specialized. It can then reprogram the same cell to take on a new role.

"If we understood how this works, we could reverse the differentiation process in skin cells, for example, to the point where we could transform them into neurons, or into liver cells," he says.

The secret lies in the oocyte's genes, which carry the instructions that regulate cell development and function. As part of a Canadian Research Chair in Animal Genomics, Dr. Sirard is using gene mathematics and comparative studies to isolate the genes in question.

"Very simply, we take all the genes that are in the oocyte of a cow, and subtract the genes expressed in the liver, kidney and other tissue," he says. "We end up with a small portion of genes that are unique to the oocyte, but there are still more than a thousand of them."

By comparing genes from the oocyte of a cow with those of other animals, Dr. Sirard hopes to isolate the genes that are expressed in the oocytes of all animals, including humans. Then he can sequence those genes and determine their role in the body.

The research has many applications for treating disease and rebuilding cell tissues. "For people with Parkinson's, you need to reprogram the nerve cells to secrete dopamine, a chemical substance that affects movement, emotional response, and the ability to experience pleasure and pain," he says. "People who are diabetic need their pancreatic cells engineered to stabilize insulin production and function."

Eventually, oocytes could even regrow pieces of our bodies using our own cells. "We could rebuild your kidney, instead of trying to get one from a donor," says Dr. Sirard.

With the strong support that I receive from Canadian governments, I can do fundamental research that will create applications. It's normally there that we create the highest value in new intellectual property.

DR. MARC-ANDRÉ SIRARD, DIRECTOR, RESEARCH CENTRE IN REPRODUCTIVE BIOLOGY, LAVAL UNIVERSITY

A BETTER MEDIUM FOR PROTEIN PRODUCTION

Most companies that make recombinant proteins use the mammary glands of cows, sheep or goats as manufacturing plants. In a new application of an existing technology, TGN Biotech—founded by Dr. Marc-André Sirard and his colleague Dr. François Pothier—has found a way to use the seminal glands of pigs.

The technique, called Semenesis, uses transgenic technologies to modify the pig's seminal vesicle gland to produce a desired protein in the semen. The semen is then collected and the specific protein purified.

"It's better than milk—it's very clean, there is no bacteria," says Dr. Sirard. "The liquid is very soft on proteins because it's there to protect sperm cells."

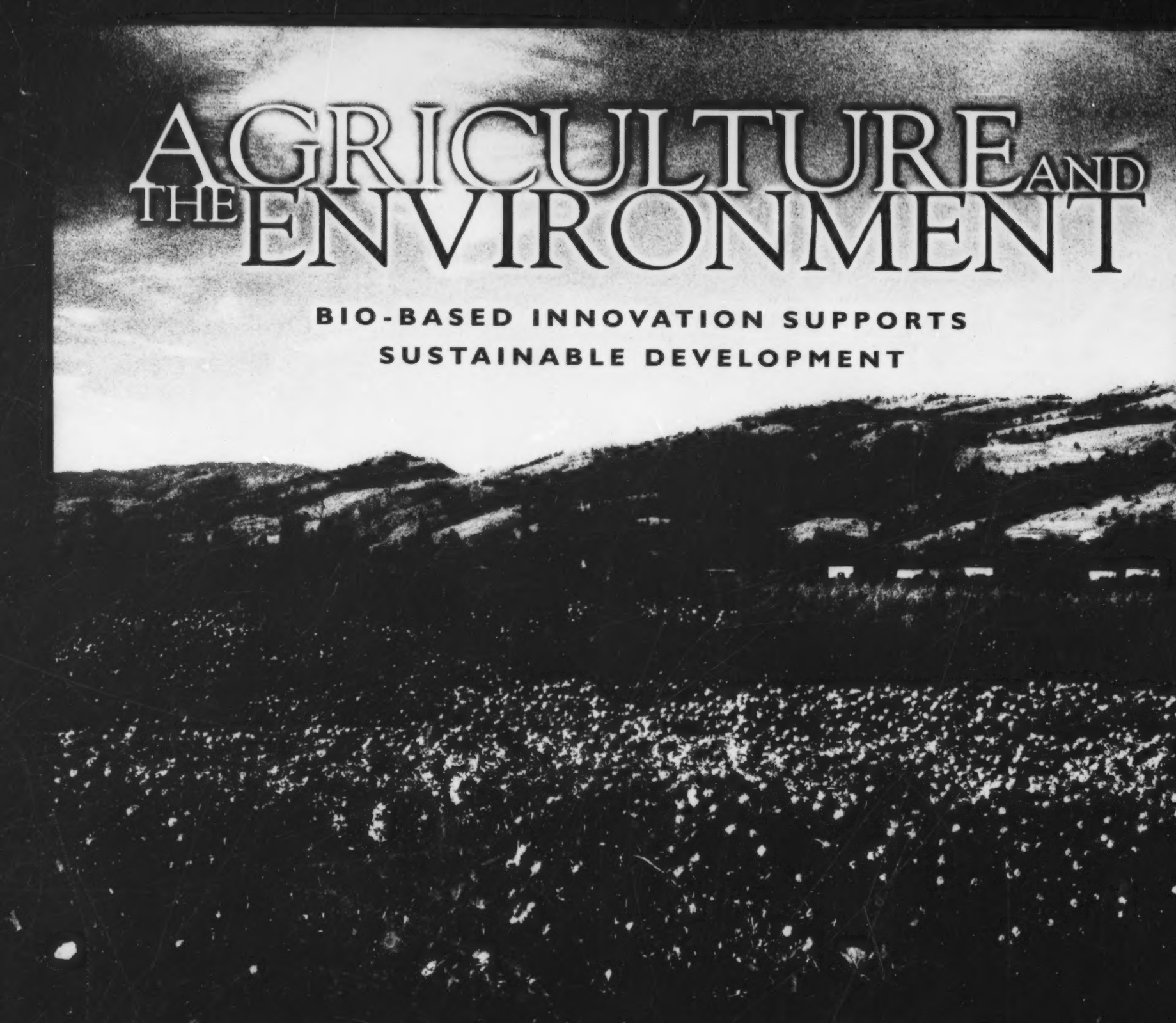
The technique is also economical, because pigs are inexpensive to raise and produce 200-500 ml of semen per day. The semen is harvested painlessly, and much more easily than harvesting milk from a sow.

Dr. Sirard originally founded the company to keep young scientists from going to the United States to seek work, but also sees a significant global market for the Semenesis technology.

"There is a huge shortage worldwide in the capacity to produce complex proteins for drug manufacturing," he says. "It's very timely for a company to provide this expertise."

AGRICULTURE AND THE ENVIRONMENT

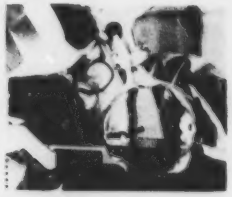
BIO-BASED INNOVATION SUPPORTS SUSTAINABLE DEVELOPMENT



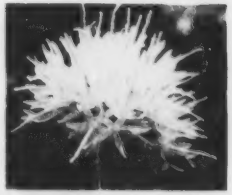
WITH ITS LARGE LANDMASS AND STRONG AGRICULTURAL TRADITION, CANADA IS WELL EQUIPPED TO TAKE A LEAD POSITION IN THE GLOBAL BID TO DEVELOP NEW PLANT VARIETIES THAT BENEFIT FARMERS AND CONSUMERS.

BUT CANADIAN SCIENTISTS APPROACH AGRICULTURAL BIOTECHNOLOGY FROM A MUCH BROADER PERSPECTIVE—ONE THAT ENCOMPASSES ENVIRONMENTAL SCIENCE AND INDUSTRY REQUIREMENTS. SINCE THE MID-1900S, CANADA HAS TAKEN A KEEN INTEREST IN HARNESSING CROP PLANTS, PLANT AND FORESTRY RESIDUES AND OTHER SOURCES OF BIOMASS TO MANUFACTURE VALUABLE INDUSTRIAL PRODUCTS INCLUDING PHARMACEUTICALS, ENERGY SOURCES, POLYMERS AND STRUCTURAL FIBRES, LUBRICANTS AND FINE CHEMICALS. SUCH PRODUCTS ARE INHERENTLY RENEWABLE, SUSTAINABLE AND OFTEN NON-POLLUTING.

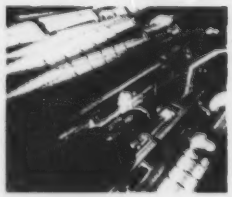
CANADIAN INNOVATION IN AGRICULTURE AND THE ENVIRONMENT



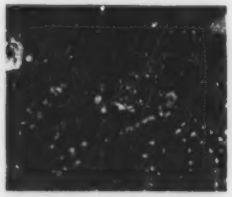
Ocean Nutrition Canada is one of the world's first firms to recognize the therapeutic potential of fisheries byproducts, such as omega-3 fatty acids and glucosamine. And the company is actively searching for more natural products with healing powers.



Dragline silk, the single-protein thread found in the radiating spokes of a spider web, is five times stronger by weight than steel. But spiders won't spin silk in cramped quarters. Dr. Jeffrey Turner asked: *what if you produced the protein in a different factory?*



With visions of tapping into pulp and paper byproducts, Dr. James Kutney helped establish Forbes Medi-Tech Inc. in 1993. The company now holds nearly 100 patents and produces everything from cholesterol-busting food additives to prescription drugs.



Calgary-based SemBioSys Genetics Inc. is harnessing oilseeds to slash the production costs of genetically engineered proteins used in the pharmaceutical, cosmetics, nutritional products and other industries.

Every day, Iogen Corporation's plant on the outskirts of Ottawa turns 40 tonnes of agricultural waste into bioethanol fuel. Iogen's enzyme-induced process extracts energy from agricultural leftovers while leaving the cream of the crop for food production.

In the 1950s, Canadian scientists responded to a shortage of edible oils by extracting seed oils from plants such as rapeseed and flax. By developing and applying the advanced technologies of the day, they eventually developed a rapeseed variety with low erucic acid in the seed oils, making it suitable for human consumption, and low glucosinolates in the meal, thereby creating a non-toxic alternative for animal feed. They dubbed the new variety *canola*—now commonly referred to as the Cinderella crop that generates annual economic activity of more than CAD$2 billion.

More recently, Canada has produced numerous plant varieties with novel traits that benefit farmers such as increased yield, resistance to insect or fungal pests, and tolerance to herbicides or with traits that benefit consumers such as healthy oil profiles, easy-to-digest fibre, and enhanced nutritional value. Most of these new plant varieties are grown for consumption by humans or domestic animals, as food or feed. In addition, Canadian researchers have been applying genetic technologies to prevent infectious diseases in livestock and improve animal production.

At the same time, Canada's agricultural and environmental research and industrial sectors have been actively pursuing a completely different direction. The aim of this work is to harness the biological and chemical energy of living things, rather than to keep expending non-renewable resources. Today, plants and animals are being used to produce valuable industrial products—such as drugs, proteins and medicinal products.

Fueled by the growing public realization that non-renewable, carbon-based resources are not limitless, and that alternative sources of raw materials must be found to sustain future global development, R&D activity in these areas is expected to increase significantly in coming years.

The Government of Canada supports innovation in these vital fields through a number of departments and agencies. Collectively, Natural Resources Canada, Agriculture and Agri-Food Canada, the National Research Council and Environment Canada are exploring new opportunities in biomass conversion, industrial uses for plants and animals, and processes that reduce greenhouse gas emissions and atmospheric carbon dioxide.

As it becomes more fully developed, the Canadian bio-based products industry will generate tremendous economic benefits for farmers, forest product companies, energy producers and chemical manufacturers. Rural areas will benefit as bio-based manufacturing facilities are established near supply sources, providing new revenue streams for farmers and cash flow for other rural development initiatives. Moreover, biotechnology will allow more of Canada's land base to be used for industrial and environmental purposes. Scientists have already developed plant varieties, such as hybrid poplar and switch grass, that thrive in marginal agricultural areas and low-grade forest regions.

Modern biotechnology has an important role to play in the emerging economy, as plants are engineered to: produce components that are easier to extract and purify; provide valuable industrial compounds such as polymers; and thrive in marginal conditions. The advent of bio-based products in the next few years will help ensure a continuous supply of renewable raw materials and energy, while reducing the production of greenhouse gases and global warming.

At the current rate of consumption growth, the world's known and estimated petroleum reserves will be exhausted within the lifetime of the current generation. In addition to improving food and feed sources, Canada is well on its way to demonstrating the viability—and sustainability—of alternative sources of energy. Turn the page to see how we plan to do it.

Forestry byproducts

SERVE UP NATURAL HEALTH BENEFITS

WHERE INDUSTRY INSIDERS SAW ONLY WASTE, ORGANIC CHEMIST DR. JAMES KUTNEY RECOGNIZED ENORMOUS POTENTIAL.

When Dr. James Kutney made British Columbia his home, he realized that the largest industry in the province was burning and burying a tremendous asset. Each time the pulp and paper mills processed a log, they threw away raw materials that could be used to produce important, and lucrative, biologically active compounds.

"Everyone knows that this is one of the drawbacks of the forestry industry—they don't know how to use the byproducts they produce," says Dr. Kutney.

With visions of tapping into a readily available resource, Dr. Kutney helped establish Forbes Medi-Tech Inc. in 1993. The company now holds nearly 100 patents—to produce everything from cholesterol-busting food additives to prescription drugs—and boasts a strong track record for innovation in unconventional areas.

While his colleagues in the University of British Columbia's chemistry department ordered fine-grade reagents for their research, Dr. James Kutney excitedly cracked open large barrels of fatty, pungent sludge.

The shipments came from local pulp mills, where the process of digesting wood chips to create pulp creates a frothy white substance known as 'soap' or 'tall oil'. The byproduct is cheap and plentiful: the average mill produces thousands of tonnes of tall oil per year.

"This stuff was just being burned, and I thought this was a real waste," says Dr. Kutney, Vice President of Scientific and Research Development, Forbes Medi-Tech Inc. "Tall oil contains high concentrations of plant sterols—called phytosterols—that have great pharmaceutical potential. I realized there could be considerable revenues derived from these byproducts."

Dr. Kutney knew something forestry workers didn't: bacteria could degrade phytosterols to create the raw materials for steroid-based drugs, such as birth control pills and anti-inflammatories. Throughout the 1980s, he toiled to perfect processes for extracting and bioconverting phytosterols.

During that period, an even more audacious—and potentially lucrative—idea occurred

EMERGING MARKETS FOR FUNCTIONAL FOODS AND NUTRACEUTICALS

Calcium-fortified orange juice and Echinacea drops are two hot products in our increasingly health-conscious society.

Functional foods are defined as recognizable, conventional foods containing ingredients that provide additional health benefits—such as calcium to reduce the risk of osteoporosis. Nutraceuticals are health-benefiting products isolated from foods and delivered in a medicinal form, which covers a broad range of herbal products.

"The growing popularity of functional foods and nutraceuticals is driven by increasing healthcare costs and people's perceptions about how to improve their longevity and quality of life," says Charles Butt, President and CEO of Forbes Medi-Tech Inc.

Statistics for these young industries are difficult to establish, but Agriculture and Agri-Food Canada estimates the current market at $1 to $2 billion in Canada, and likely more than $15 billion in both the United States and Europe.

We're showing that there is more and more you can do with the byproducts of the forestry industry. I think this is exciting, since Canada has traditionally been more primary resource-based but lacking in secondary industries.

DR. JAMES KUTNEY, VICE PRESIDENT, SCIENTIFIC AND RESEARCH DEVELOPMENT, FORBES MEDI-TECH INC.

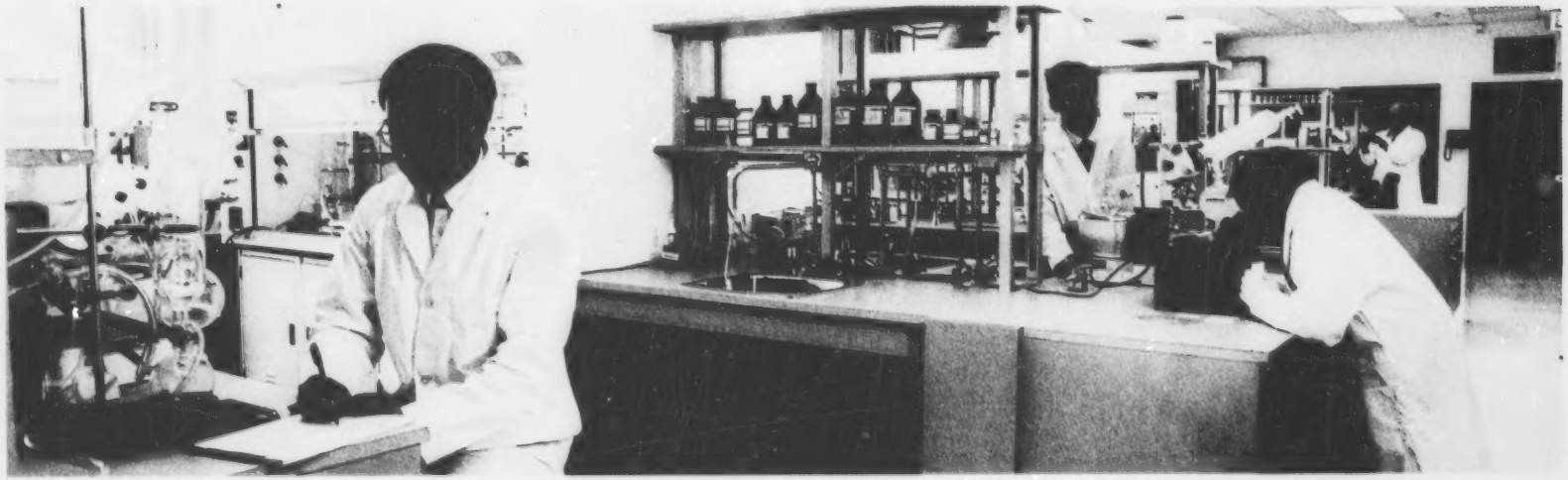
to Dr. Kutney. He remembered that in the early 1950s, the pharmaceutical giant Eli Lilly and Company briefly marketed phytosterols to combat high cholesterol. The concept was relatively simple: phytosterols help stabilize plant cell membranes in much the same way as cholesterol stabilizes human cell membranes, and both molecules have nearly identical structures. Eli Lilly found that phytosterols could be used to block absorption in the small intestine, ultimately reducing the amount of cholesterol circulating through the bloodstream and clogging arteries.

Knowing that at least half of North Americans have elevated cholesterol levels, Dr. Kutney saw an excellent opportunity to revive the idea. In 1993, he was approached by Tazdin Esmail and Egon Novak, two colleagues who indicated an interest in developing both aspects of phytosterol production. Forbes Medi-Tech was established with two business objectives: to produce raw materials for steroid-based drugs and to create cholesterol-fighting food additives.

"The Eli Lilly product failed because you had to take so much of it, at least seven grams a day, to get a real effect," says Dr. Kutney. "We found that our phytosterols were much more potent—you only needed 1.5 grams to get a cholesterol-lowering effect."

Forbes ran a clinical trial in 1999, supplementing the diet of hypercholesterolemic men with a 1.8g daily dose of Phytrol™—the brand name of their cholesterol-fighting phytosterol. By the end of one month, the average LDL-cholesterol levels of subjects dropped by 15 per cent. This low-density lipoprotein cholesterol is known as 'bad' cholesterol because of its tendency to form plaque deposits that restrict arterial blood flow.

"Phytosterols are clinically proven for reducing LDL and total cholesterol, and therefore cardiovascular disease," says Jerzy Zawistowski, Forbes' Vice President of Functional Foods and Nutraceuticals. "I'm not aware of any other



manufacturer of a functional food in Canada with solid support from clinical trials."

In addition to its potency, Phytrol has another major advantage over competitor products. Unlike other cholesterol-lowering sterols, it doesn't have to be incorporated into fat-based matrices such as margarine or salad dressings, which is important for consumers looking to avoid high-fat products. Rather, Forbes opted to include the sterols in daily staples and briefly partnered with Novartis to test the product line.

"The test market results of our cereals and cereal bars were good in terms of consumer uptake and consumer perception," says Charles Butt, Forbes' President and CEO. Unfortunately, when Novartis decided to get out of the functional food business, "the product line became a classic, corporate orphan child."

Phytrol is now being marketed in the United States by dietary supplement companies such as Pharmavite and Twin Laboratories, but Forbes remains confident of the product's broad potential and is looking for other major partners. In a joint venture with Chusei (U.S.A.) Inc., a subsidiary of Chusei Oil Co. Ltd., Forbes recently built one of the largest sterol-production facilities in the world—a 1,000-tonne capacity plant near Houston, Texas.

As a follow-up to the functional foods line, Forbes is also venturing into the pharmaceutical industry with a cholesterol-lowering compound named FM-VP4. Pre-clinical studies show that FM-VP4 has tremendous potential; Phase I clinical trials at the University of Amsterdam are scheduled for completion mid-2002.

Over the past 20 years, Dr. Kutney has received considerable support from government granting agencies such as the Natural Sciences and Engineering Research Council and the Science Council of British Columbia.

The nutraceutical and functional food market will definitely increase. There are three hot areas right now—cardiovascular, digestive, and women's health. We have a strong product for cardiovascular health, so the future looks good.

CHARLES BUTT,
PRESIDENT AND CEO, FORBES MEDI-TECH INC.

PHYTROL™ APPROVED FOR U.S. MARKETS

Phytosterols—and Phytrol™ in particular—stand out in the functional food market because of the clinical data supporting their cholesterol-reducing claims. In fact, nearly 100 clinical studies worldwide have delivered positive results.

In May 2000, Phytrol was cleared for sale in the United States by the Food and Drug Administration (FDA) under the *Generally Recognized As Safe* notification process. The FDA subsequently issued an interim rule allowing foods fortified with 'sterol esters' to make health claims on their labels. Forbes Medi-Tech Inc. has submitted an application to have the health label claim ruling extended to include free sterols such as those in Phytrol. A decision is pending.

Mining the

FOR NUTRITIONAL GOLD

OCEAN NUTRITION CANADA GOES UNDERWATER TO DISCOVER NEW BUSINESS OPPORTUNITIES.

With its coastal Nova Scotia locations, guaranteed access to fresh raw materials, and talented research team, Ocean Nutrition Canada is in an ideal position to dominate the emerging marine-based nutritional ingredients industry. The young biotech firm is one of the world's first to recognize the commercial potential of fisheries byproducts with therapeutic properties such as omega-3 fatty acids and glucosamine. And Ocean Nutrition is actively searching for more natural products with healing powers. Because only a tiny fraction of marine compounds have been identified and characterised, the ocean's the limit when it comes to the company's future growth.

Imagine getting the health benefits of eating two fish per week from everyday staples such as bread, orange juice, soup or salad dressing. That's the kind of h. ady vision driving the rapidly growing "functional foods" industry—estimated to be worth up to $57 billion worldwide by the year 2004—and one that Nova Scotia-based Ocean Nutrition Canada is poised to exploit.

Launched in 1996 by Clearwater Fine Foods, the largest privately held seafood company in Canada, Ocean Nutrition Canada was conceived by Clearwater's owner and CEO, John Risley. In the early 1990s, Mr. Risley started wondering about the commercial potential of fisheries byproducts. When the U.S. television show *60 Minutes* produced a documentary alleging that shark cartilage had anti-cancer benefits, Mr. Risley hired two scientists to find out whether the medical claims had

any validity. It turns out they didn't: shark cartilage supplements have no impact on human cancers.

But this exercise helped persuade Mr. Risley that there may be other marine compounds in the fisheries waste stream—with real nutritional or therapeutic value. In the mid-1990s, a Nova Scotia Crown corporation, InNOVAcorp,

OCEAN NUTRITION CANADA'S SEASIDE APOTHECARIES

"Early on, we realized the need to ensure the safety and efficacy of our products," says general manager Robert Orr. "To support that requirement, we have assembled a highly competent group of people including research scientists, engineers and technical production professionals."

Ocean Nutrition boasts the most advanced privately owned facilities for analysing marine natural products in North America, which allows the company to apply a pharmaceutical model to the development of its marine compounds.

"When we isolate and characterise bioactive compounds, we know what works, how it works, and we can ensure that the right amount of bioactive material is there every time," he says. "Our ability to control the active compound in any extract is critically important, especially for toxicological or human clinical trials."

introduced him to Laer Products Ltd., a Cape Breton-based manufacturer of omega-3 fish oils for the veterinary market. Risley ended up buying Laer Products as a jumping-off point for his new business strategy.

Today, Mr. Risley's dream is a reality. Drawing on a wealth of human resources in the Halifax area, such as the National Research Council's Institute for Marine Biosciences and Dalhousie University Medical School, Clearwater has built a 170-employee company with a team of 40 marine scientists. Ocean Nutrition Canada claims to be the "world's leading researcher, manufacturer and marketer of marine natural products to the global marketplace," a position strengthened by its steadily climbing sales of dietary supplements and functional food applications. The company's two primary products are: heart-healthy omega-3 fish oils, harvested from salmon, sardines and anchovies; and the anti-arthritic compound glucosamine, an extract from crab and shrimp shells. Ocean Nutrition sells its marine compounds mainly to nutritional products companies and major food suppliers.

And unlike its competitors, Ocean Nutrition Canada is actively mining the oceans for more natural compounds with potential health and nutritional benefits. "No one else in the world is doing what we're doing," says general manager Robert Orr. "We have competitors worldwide, for example, in the omega-3 business and in the glucosamine business. But no one else is taking the same scientific approach to finding new products: screening compounds, testing them, then isolating and characterising their properties."

Ocean Nutrition Canada focuses on key 'Western society' medical conditions such as diabetes, cardiovascular diseases, high blood pressure and arthritis. "We're looking for natural compounds with no side effects that have a positive impact on these diseases," explains Mr. Orr. The company currently has about a dozen products at various stages of development including compounds that boost the immune system, lower cholesterol, reduce blood pressure, and impact both cholesterol and triglycerides at the same time.

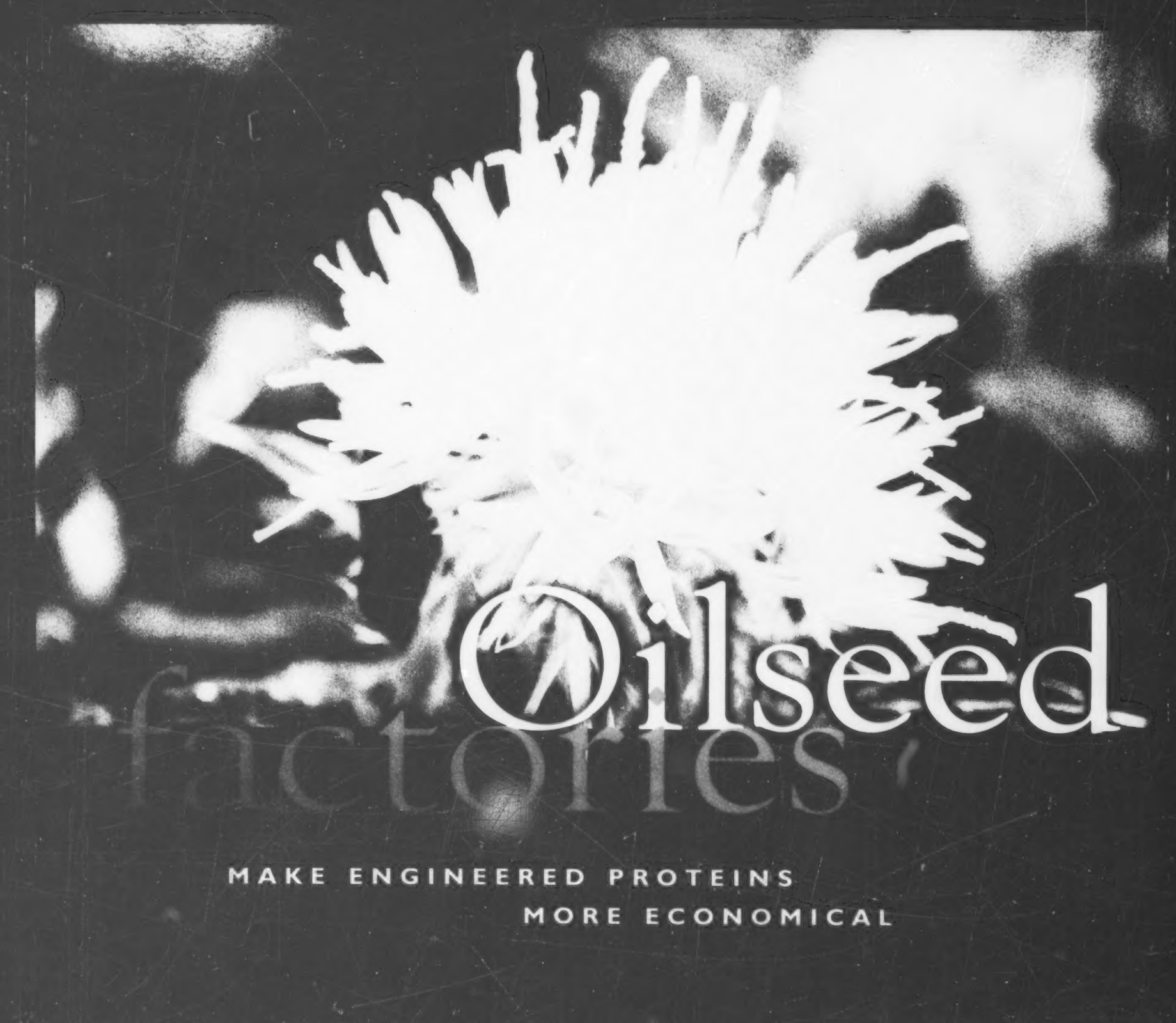
"Our goal is to sell these ingredients as dietary supplement ingredients in the short term," says Orr. "But over the longer term, we believe in promoting a more natural approach to maintaining wellness by incorporating these nutrients into the food system—such as with calcium-fortified orange juice. For example, maybe we can introduce completely safe ingredients into the favourite foods of people with hypertension, which will allow them to lower their blood pressure through their diet so they don't have to pop pills every day."

IN PRAISE OF OMEGA-3

"Omega-3 from fish oil can reduce the risk of sudden cardiac death by up to 81 per cent," declares the *New England Journal of Medicine* (April 2002). "Eating fish cuts heart attack risk, studies show," declares *The Globe and Mail*, while CNN asks, "The benefits of fish without the fish?" Such headlines routinely trumpet the benefits of Ocean Nutrition Canada's main product.

Scientific studies suggest that omega-3 fish oils decrease triglyceride levels, reduce blood clotting, lower blood pressure, decrease blood viscosity, help prevent arrhythmia, and reduce joint and muscle inflammation. They also appear to reduce the risk of brain disorders and may even enhance memory, cognition, awareness and mood.

According to the *Journal of Nutrition*, "The North American diet lacks adequate levels of omega-3 fatty acids to provide optimum health because they are not present in most common foods." For Ocean Nutrition Canada, this all translates into great expectations of a healthy bottom line.


Oilseed
factories
MAKE ENGINEERED PROTEINS
MORE ECONOMICAL

A MOLECULAR FARMING METHOD DEVELOPED BY DR. MAURICE MOLONEY EXPLOITS BASIC PHYSICS TO REVOLUTIONIZE THE PRODUCTION AND PURIFICATION OF COMMERCIAL PROTEINS.

Scientific advances have dramatically increased the number of proteins with commercial potential, but the protein products pipeline isn't flowing the way it should. For smaller biotech firms in particular, the daunting costs of building production facilities—combined with expensive purification processes—slow the pace of bringing proteins to market.

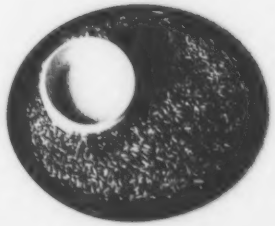
SemBioSys Genetics Inc., a Calgary firm built upon Dr. Maurice Moloney's love affair with oilseeds, has found a way to slash the costs of manufacturing genetically engineered proteins used in the pharmaceutical, cosmetics, nutritional products and other industries. The company believes it has a globally applicable solution to help biotech companies lower production costs, based on the unique properties of oilseeds.

Around the world, genetic engineering is accelerating the development of novel proteins with commercial potential. But for the companies that need genetically engineered compounds, splicing a protein gene into a host bacterium, plant or animal species is just the first step. In many cases, the most fiscally challenging part—accounting for 80 to 90 per cent of total production costs—involves isolating and purifying the end product.

Enter SemBioSys Genetics Inc., which is pushing the frontiers of plant biotechnology to deliver cost-effective protein production and purification services across the biotech industry. The privately owned, 65-employee company has developed a new approach—the StratoSome™ Biologics System—in which recombinant proteins are grafted to oilseed proteins found in safflower. After harvest, the desired proteins are easily extracted with the safflower oil.

This technique promises to substantially lower the cost of producing, collecting and purifying commercial peptides and proteins that other companies require to generate vaccines, pharmaceuticals, industrial enzymes, cosmetic ingredients and nutritional products. In the process, SemBioSys' technology may create exciting opportunities for oilseed farmers.

"We think that we'll be able to rewrite the whole story of manufacturing drugs," says



PUTTING SAFFLOWER ON DOUBLE DUTY

Traditionally harvested for its oil, the safflower seed may someday be better known as the ideal protein factory.

Firstly, safflower is readily available. It thrives in both the northern and southern hemispheres. With few weed varieties found in the western hemisphere, safflower is also easy to contain—which reduces the risk of any foreign genes being carried through the environment.

According to Dr. Maurice Moloney, the safflower is easy to modify in the lab; as well, studies show that genetically engineered proteins are stable in transgenic safflower seeds for long periods of time.

MOLECULAR FARMING OPENS VAST NEW MARKETS

With its promise of higher revenues per hectare and immunity from unpredictable commodity markets, molecular farming offers a bright future for many farmers. The emerging agribusiness aims to transform traditional crop plants into manufacturing facilities for products such as industrial oils, enzymes, plastics, therapeutic proteins and vaccines.

"If plant molecular farming replaces some forms of conventional manufacturing, it could easily become a $10 to 15 billion business in 10 years," predicts SemBioSys founder Dr. Maurice Moloney. "Producers are very enthusiastic."

Dr. Maurice Moloney, the company's founder and Chief Scientific Officer. "There are hundreds of exciting new medications in development, but they're very expensive to produce. That's where we come in. Using our technology, we are confident that protein production facilities can be built for a fraction of what they cost now."

As a result, SemBioSys is confident about its future. "Five years from now, we want to be the world's leading supplier of transgenic proteins for the pharmaceutical market," says Andrew Baum, SemBioSys President and CEO. "In ten years, we want to be recognized as a leading, fully integrated biopharmaceutical business. We believe our technology is that powerful. A lot of companies are involved in the transgenic production of proteins. But we're the only one that simultaneously addresses both the purification and bulk production of proteins, while offering other benefits such as enhanced protein formulations for oral and topical applications."

SemBioSys was founded in 1994 as a spin-off from the University of Calgary, where Dr. Moloney holds the Industrial Research Chair of Plant Biotechnology, sponsored by the Natural Sciences and Engineering Research Council of Canada and Dow AgroSciences. After several years in the 1980s with the U.S. firm Calgene Inc., Dr. Moloney came north to teach and conduct university research. SemBioSys emerged from his early analysis of the inner workings of canola seeds. "When I was with Calgene, I got very attached to canola seeds. Later, we found

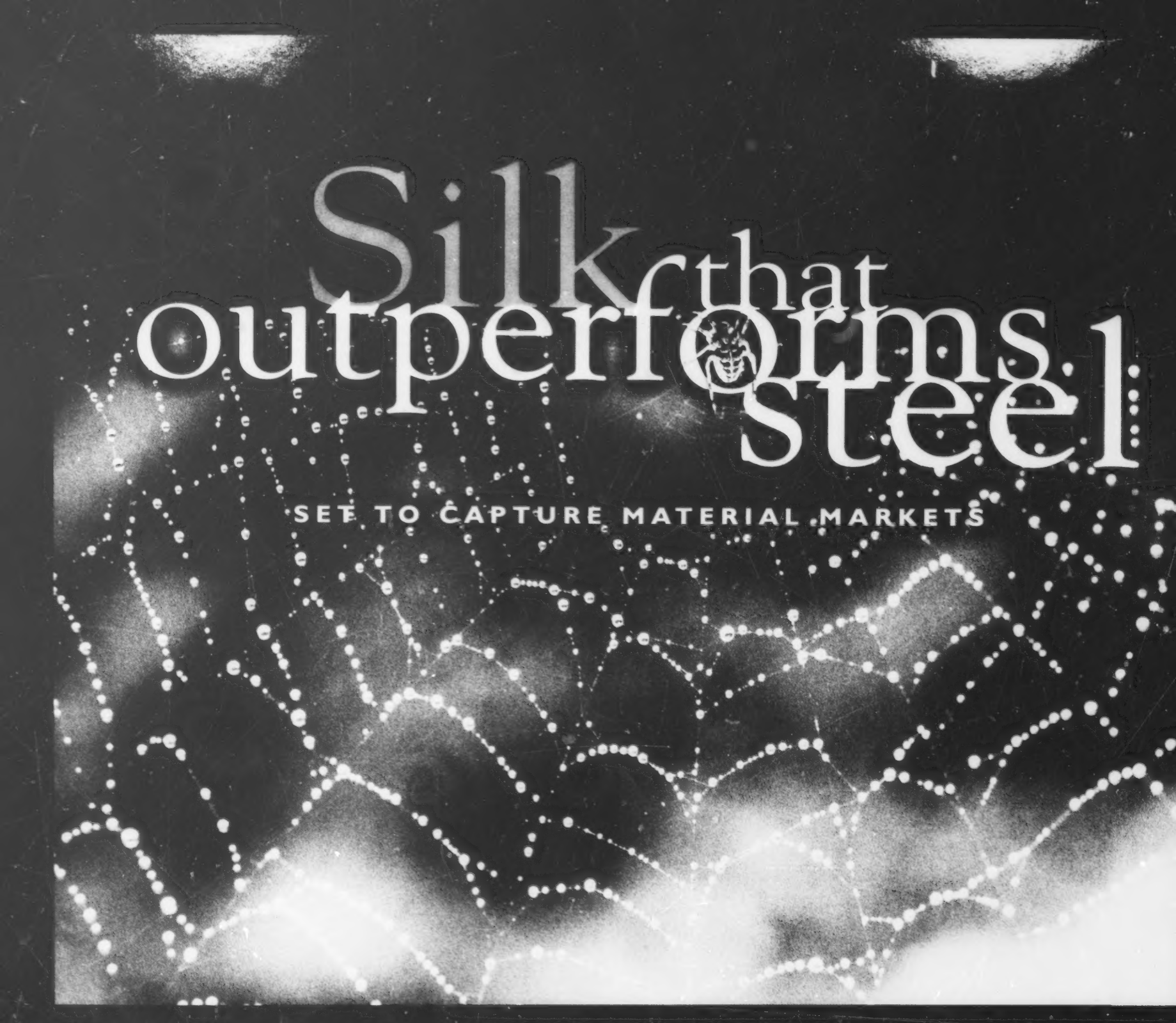
that safflower shared canola's virtues but had other advantages, so now I love it even more."

Although most plant proteins tend to be water soluble, oleosin proteins found in oilseeds have a higher affinity for oil. The role of oleosins is to collect the oil droplets produced by crops such as safflower and canola. Dr. Moloney discovered that when recombinant protein genes are spliced to oleosin genes, the expressed proteins end up adhering to oleosins inside safflower seeds. And because oil is lighter than water, it's relatively easy to extract and isolate oleosins—along with any attached proteins—in a purified form.

"When the plants mature, we simply harvest the seeds, and collect and purify the protein in much the same way as you would separate cream from milk," explains Mr. Baum. So far, SemBioSys has demonstrated this technology with more than 25 different proteins including anti-obesity compounds, cosmetic ingredients, therapeutic products and proteins used in aquaculture.

With its efficient, cost-cutting technology, SemBioSys has had little trouble attracting interest and capital from both private and government sources. Current investors include Bay City Capital, Business Development Bank of Canada, Dow AgroSciences, Royal Bank Ventures Inc., the University of Calgary, and Ventures West Capital Ltd.

What's more, SemBioSys is already staking its claim in the market. So far, its clients include the agribusiness giant Syngenta, Metabolic Pharmaceuticals of Australia, and a multinational fine chemicals manufacturer.


Silk that outperforms steel
SET TO CAPTURE MATERIAL MARKETS

MOLECULAR GENETICIST DR. JEFFREY TURNER, FOUNDER AND CEO OF NEXIA BIOTECHNOLOGIES INC., FINDS A WAY TO SPIN CELLULAR SIMILARITY TO HIS ADVANTAGE.

With an inherent genius for engineering, a spider spins seven types of silk: one for wrapping eggs, one for wrapping prey, and five for web construction. Dragline silk, the single-protein thread used to create the web's radiating spokes, has a tensile strength of 400,000 pounds per square inch and is five times stronger, by weight, than steel.

But the territorial and aggressive nature of spiders severely limits the supply of spider silk. Unlike silkworms, spiders will not produce in cramped quarters. Dr. Jeffrey Turner looked at the potential market for spider silk and asked a basic question: *what if you produced the protein in a different factory?*

"Spider silk is a material science wonder—a self-assembling, biodegradable, high-performance nanofibre structure one-tenth the width of a human hair that can stop a bee traveling at 20 miles per hour without breaking," says Dr. Jeffrey Turner, founder and CEO of Nexia Biotechnologies Inc. "Spider silk has dwarfed man's achievements in material science."

Spider silk is considered a fine 'denier' fibre—a yarn weighing only one gram for each 9,000 metres.

The properties of proteins first captured Dr. Turner's attention while he was teaching molecular biology—an area of science that focuses on finding patterns in fine detail—at McGill University (Montréal, Québec). It is only at this level that orb spiders (which weave orb-shaped webs) and Nigerian dwarf goats reveal their similarities. By some whim of nature, spider silk glands and goat mammary glands both contain epithelial cells that manufacture and secrete large amounts of complex, water-soluble proteins. In the spider's case, an additional 'spin cycle' makes the previously soluble proteins insoluble—and the resulting fibres even more desirable.

With this in mind, Dr. Turner founded Nexia in 1993 and started building Canada's first transgenic farm animal facility. He shifted his attention to finding the gene that codes for silk protein production, then began the quest for another living system that could decipher

BREEDING SUCCESS

In January 2000, Nexia Biotechnologies Inc. announced the birth of two male BELE® goats, which have since been used to sire a growing herd of silky milk producers. The acronym stands for 'Breed Early, Lactate Early' and reflects the desired qualities of an organic spider silk factory: short generation times, multiple births, and good milk production.

The company expects first-generation female BELE goats to start producing BioSteel® milk by the summer of 2002 and recently confirmed that the silk-producing gene has been successfully transferred to the second generation of the new breed.

the spider's genetic instructions to deliver the desired product. By 1999, the company achieved its first critical milestone: Nexia's patented MAC-T mammary cell lines successfully produced fully soluble silk protein in a laboratory setting.

This encouraged the company to forge ahead with the concept of using a milk-producing herd to house Nexia's silk protein factory. The Nexia team added a single gene to the 70,000 others that regulate all aspects of goat life, in such a way that the spider gene lies dormant in every cell except the critical epithelial cells found in female mammary glands. The end result is a goat breed, known as the BELE® (Breed Early, Lactate Early) system, that produces silky milk.

But producing silk protein is only the first step in manufacturing Nexia's proposed BioSteel® product line. Once extracted from the milk, the syrupy liquid of silk proteins must be spun into fibres. Again, Nexia's aim is spider-like: the company wants to optimize its spinning processes to create a range of spider silks with different properties. Each type of spider silk is composed

It's incredible that a tiny animal found literally in your backyard can create such an amazing material using only amino acids, the same building blocks that are used to make skin and hair.

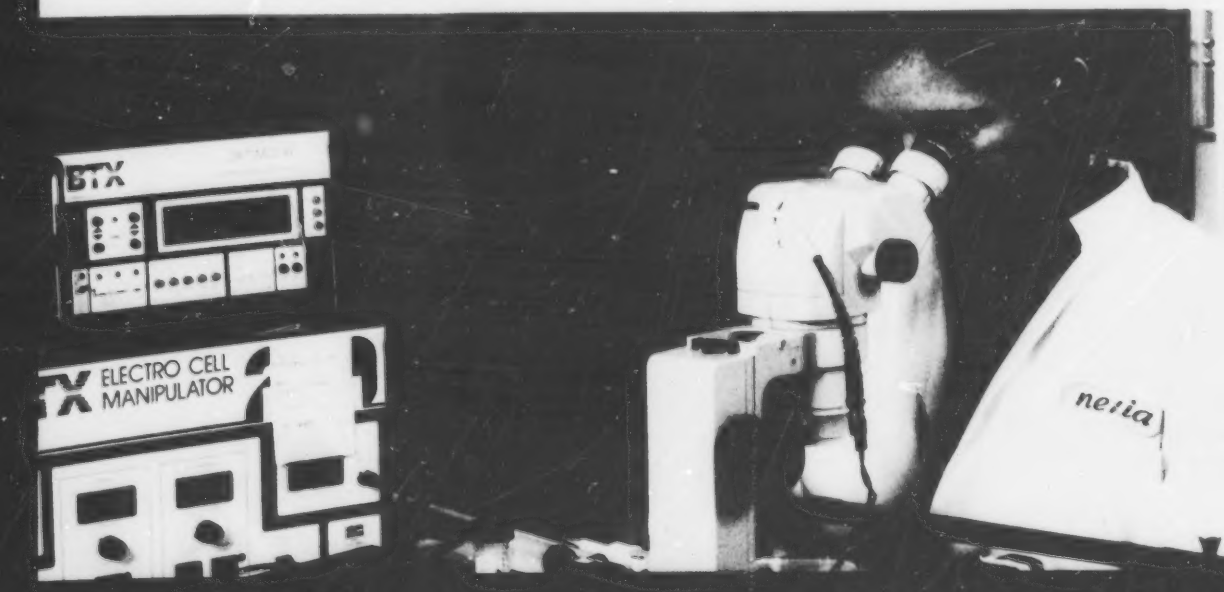
DR. JEFFREY TURNER, CEO,
NEXIA BIOTECHNOLOGIES INC.

of specific proteins coded by specific genes, which means Nexia has at least six more genes to explore. Dragline silk is coveted for its tensile strength, but 'capture silk' is stickier and can stretch up to three times its length before breaking. Ergo, Nexia sees commercial potential for several BioSteel product lines.

But it's not only the end product that holds appeal. "Using these water-based BioSteel solutions for large-scale fibre spinning would be much more environmentally friendly than using the harsh solvents typical of most synthetic fibre manufacturing," says Costas Karatzas, Nexia's Senior Vice-President of Research and Development.

Commercial spider silk is still a year or two away, but Nexia is already weaving an impressive web of support. The company raised $42.2 million in Canada's largest biotech Initial Public Offering and now trades on the Toronto Stock Exchange as NXB. It has received approximately $24.7 million of private funding from prominent investors such as MDS Capital Corp., the Ontario Teachers' Pension Plan, Société Innovatech du Grand Montréal, Royal Bank Ventures Inc., Sofinov (a subsidiary of the Caisse de dépôt et placement du Québec), the Canadian Medical Discoveries Fund, and four Asian investor groups. Nexia now has 65 highly trained employees, a centralized office and laboratories in the Montréal suburb of Sainte-Anne-de-Bellevue, and three production farms (two in Québec and one in upstate New York).

Nexia is also looking into developing other BioSteel producers, including cows and plant crops. The company is currently collaborating with the Institute of Plant Genetics and Crop Plant Research (IPK, Germany) to assess the potential of manufacturing spider silk proteins in potatoes and tobacco. The main objective is to compare production costs in various species and expand the number of silks produced.



FROM MEDICAL DEVICES TO MILITARY GEAR

The size, tensile strength, and biodegradability of BioSteel® make it an ideal material for two segments of the medical device market: wound closure systems (including vascular repair devices, homeostatic dressings, patches and glues, and sutures) and ligament prosthetic devices. Nexia Biotechnologies Inc. is currently collaborating with partners that have expertise in the technical, regulatory and clinical aspects of medical device development.

BioSteel holds equal appeal for the U.S. Army (Soldier and Biological Chemical Command) and the Canadian Armed Forces (Defence Industry Research Program of the Department of National Defence). Both groups are working with Nexia to create protective clothing such as bulletproof vests and soft-armour suits, as well as specialty ropes and nets. Early studies demonstrate that BioSteel is lighter, yet tougher than Kevlar.

Enzyme reactions

HELP CLEAN UP KEY SECTORS

AFTER 30 YEARS OF SUCCESS IN DEVELOPING INDUSTRIAL ENZYMES, RENEWED INTEREST IN CLEAN FUELS ALLOWS IOGEN CORPORATION TO RETURN TO ITS ROOTS.

Iogen Corporation has taken the idea of separating the wheat from the chaff to heart. Every day, its plant on the outskirts of Canada's national capital turns 40 tonnes of agricultural waste—wheat, barley and oat straw as well as stalks of corn—into bioethanol fuel. Iogen's enzyme-induced process extracts energy from agricultural leftovers while leaving the cream of the crop for food production.

The concept of using ethanol fuel has existed for almost as long as the internal combustion engine. But the clear benefits of bioethanol—including a 99 per cent reduction in greenhouse gas emissions*—have been overshadowed by high production costs associated with grain ethanol and the controversy of using vital food sources to create fuel resources.

Until now.

Driven by issues such as rising oil prices, heavy reliance on foreign sources, and environmental concerns, petroleum producers and consumers alike are eager to see cleaner options at the gas pump. For Iogen Corporation, it means the time for their initial *raison d'être* has finally come.

In the mid-1970s, with the world on the verge of a fuel shortage, Iogen responded by proving that enzymes could break down the sugars in plant fibre to produce clean-burning ethanol fuel. When oil prices fell and interest in alternative sources waned in the 1980s, the company looked for ways to apply its knowledge in other sectors. Iogen built an international reputation for enzyme products that improve the digestibility of animal feed and significantly reduce the environmental impact of both the pulp and paper and textiles industries.

Now, with an economically viable process in place, the world's first bioethanol demonstration plant in operation, and blueprints for a full-scale commercial plant on the table, Iogen is undeniably the centre of global attention.

Iogen never let go of its bioethanol dream. Ever aware of the need to generate a secure, domestic energy supply, the company took a serious look at raw materials and further refined its active ingredient. Iogen now starts with the fibrous portion of plants—essentially the

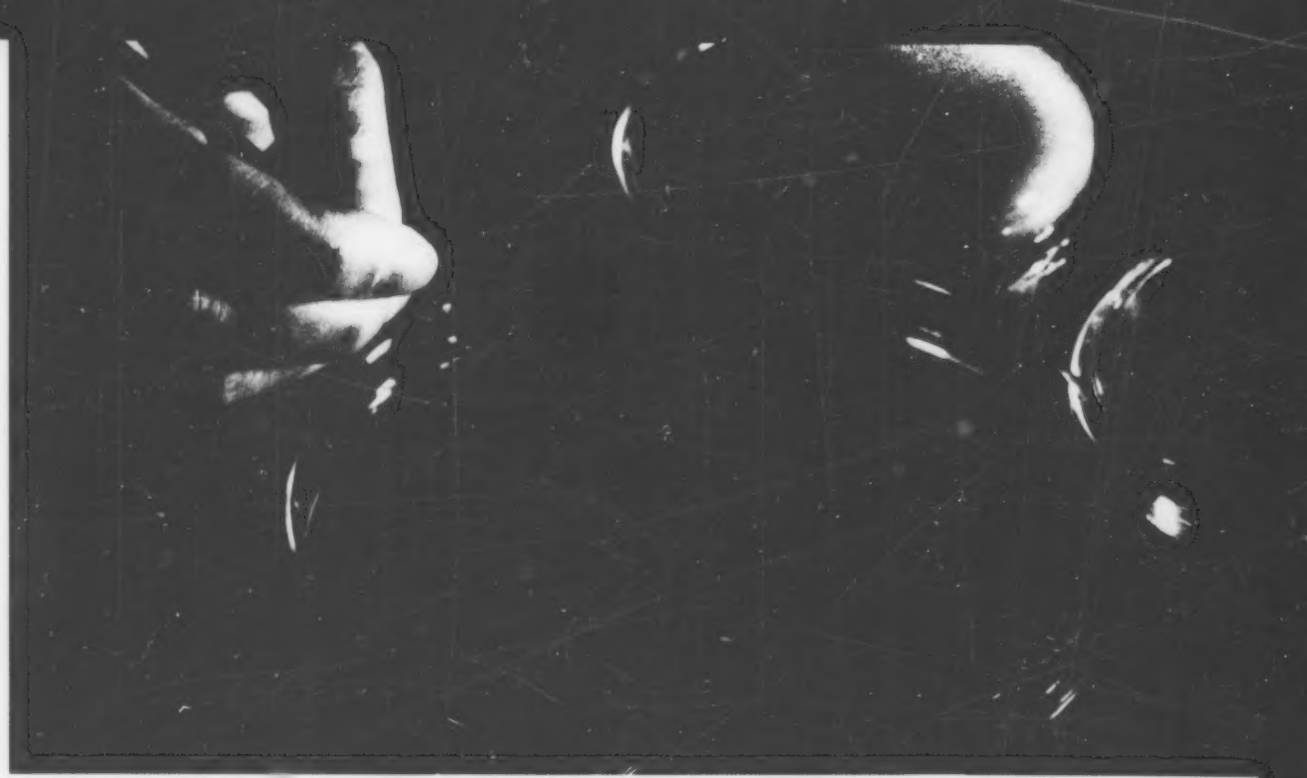
THE BENEFITS OF BIOETHANOL

Bioethanol provides practical solutions to many energy and environmental issues such as dwindling energy supplies, global climate change, and consumer demand for greener choices.

This alternative fuel makes virtually no contribution to greenhouse gas emissions. Because it contains 35 per cent oxygen, bioethanol burns more efficiently and produces up to 30 per cent lower toxic carbon monoxide emissions than regular gasoline. In fact, bioethanol actually reduces smog and local air pollution.

Because it is produced from existing agricultural residues that are widely available in Canada, bioethanol is poised to become a viable domestic source of energy. Moreover, large-scale production plants will revitalize rural communities by creating a new market for farmers and generating business opportunities for local communities.

* *U.S. Department of Energy Life-cycle Analysis*



IOGEN CLEANS UP ON BLEACHING AND STONEWASHING

Today's consumers know they want white paper and faded jeans. What they don't know is that Iogen enzymes have helped producers of both products clean up their act by replacing environmentally detrimental processes.

Iogen's BioBrite® xylanase product line helps pulp and paper companies produce high-quality products with less chlorine bleach. The active enzymes break down fibrous raw material, making it more accessible to a smaller amount of chlorine. In the process, BioBrite reduces the release of toxic dioxins known to pollute rivers and streams.

The Denabraide® cellulase line allows textile manufacturers to provide the softer, more faded jeans that consumers prefer without the environmental impact caused by pumice stones and chlorine bleaches.

Iogen supplies 90 per cent of the xylanase enzyme used in Canadian pulp mills and 10 per cent of the world supply of fading agents in the blue jeans industry.

bio-waste of farming and food production, which is much cheaper than the grains themselves but still a readily available, renewable resource. In addition, it developed a cellulase enzyme that accelerates the conversion of these plant fibres into sugars, which are then fermented and distilled into ethanol. Together, these factors put to rest the argument that bioethanol is too impractical and costly to manufacture.

That vital leap forward captured the attention of Canada's largest petroleum producer. In 1997, Petro-Canada invested in Iogen to support the development of a bioethanol validation facility. Just three years later, these two partners received additional funding from the Government of Canada to establish the world's only bioethanol demonstration plant. This plant is designed to validate equipment performance and to identify and overcome production problems prior to the construction of a $300-million full-scale commercial plant in 2004.

People usually think of bioethanol when they think of us, which is just fine. But if you read magazines or books, drink fruit juices or beer, or wear jeans or T-shirts, there's a good chance Iogen has made direct contact with some part of you during most days of your life.

BRIAN FOODY,
PRESIDENT, IOGEN CORPORATION

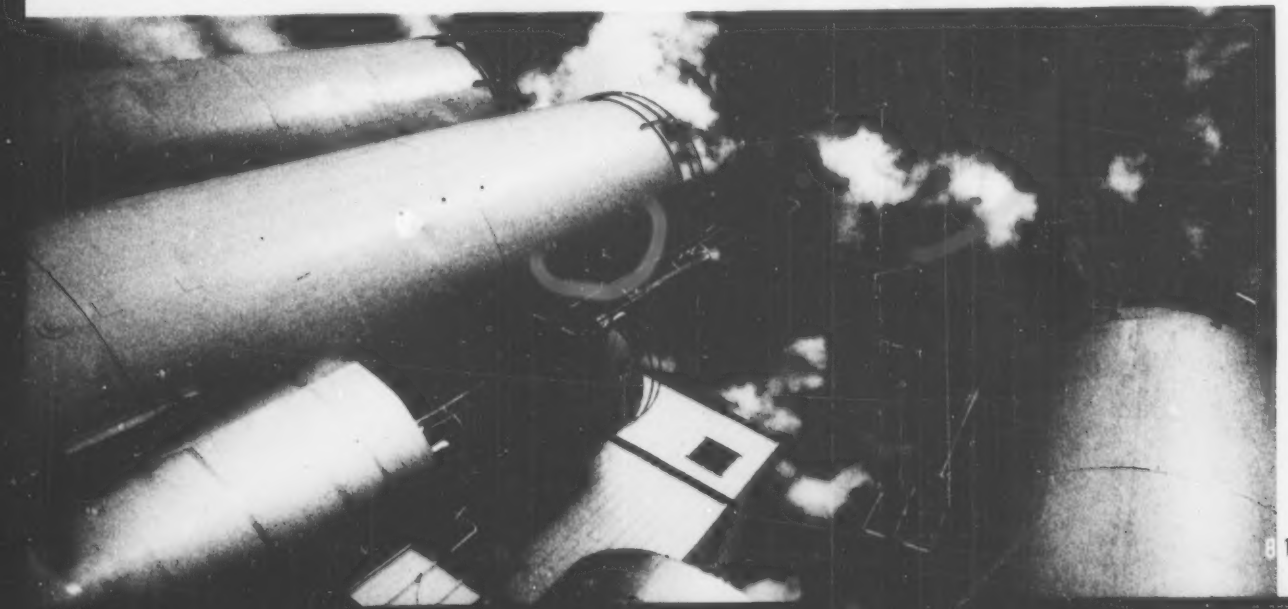
Such broad-spectrum success comes from Iogen's careful cultivation of one of the world's fastest-growing organisms. The company's Ottawa-based facilities house huge vats of fungus, which replicate quickly to supply a steady stream of enzymes. Through in-depth research of these biochemically active proteins, Iogen has found ways to dramatically increase the rate of naturally occurring biochemical reactions.

Iogen's enzymes fall into two broad classes: cellulases, which target a plant fibre constituent called cellulose; and hemi-cellulases, which modify hemi-cellulose. Within these classes, Iogen produces a wide array of task-specific enzymes that can be delivered in liquid or powder form. Depending on how they are selected and used, Iogen's enzymes can help industrial clients meet technical specifications for their products, improve processes to reduce operating costs, and increase yields from individual batches. For example, an enzyme additive may prevent fibrous material from clogging production systems or deliver an end product (such as apple juice) with greater clarity.

But Iogen's commercial offering doesn't start and end with enzymes. In recent years, the company expanded its business base by developing specialized enzyme application equipment and testing processes for the pulp industry. Iogen's remotely operated control systems regulate enzyme and acid addition in production plants across the country while also collecting vital data, used to generate productivity and quality assurance reports for individual clients.

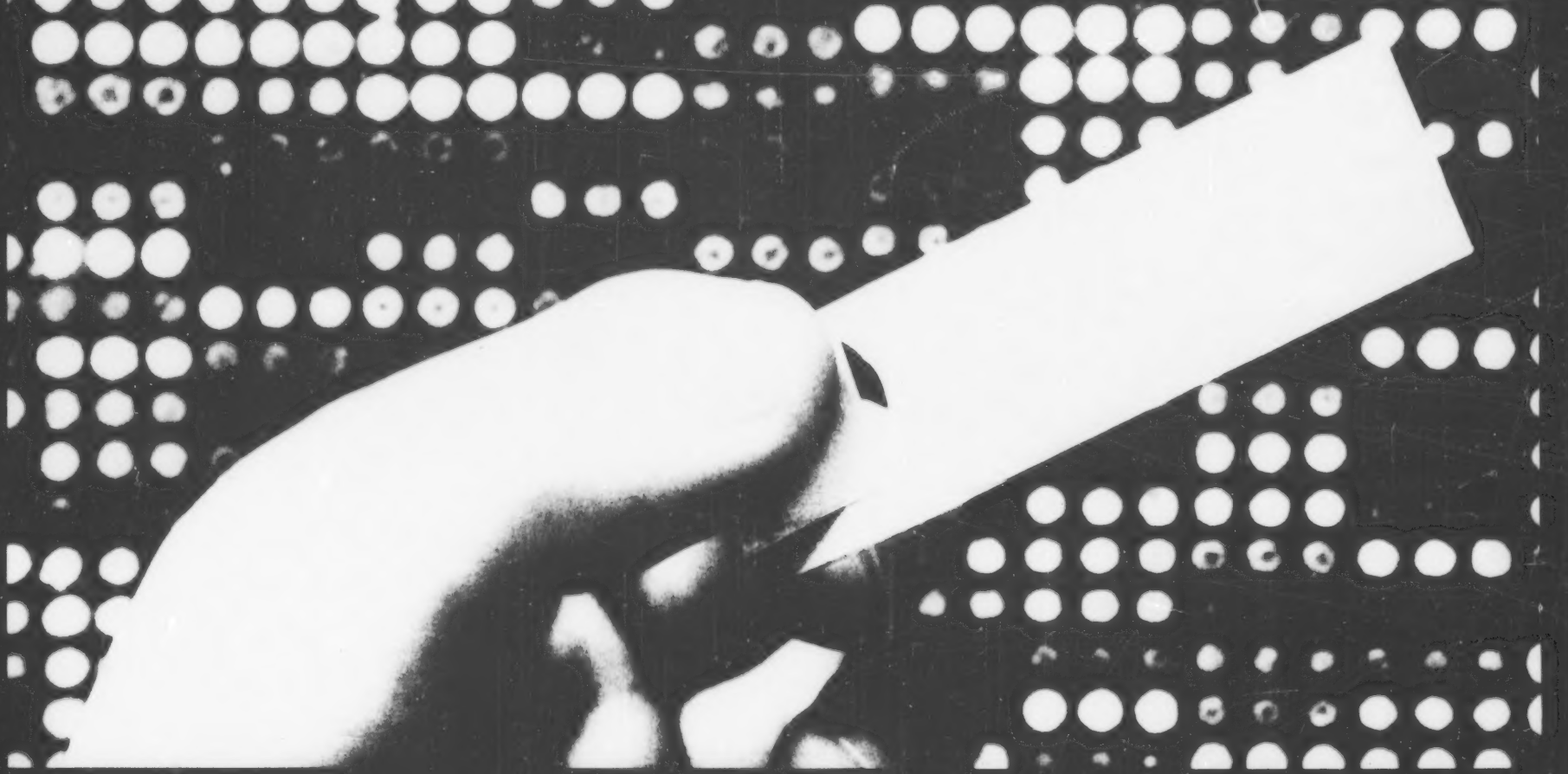
Iogen's full-service approach ultimately leads to production improvements that directly affect the bottom line in key industry sectors—all while responding to consumer demands that include cleaner streams and rivers, lower levels of air pollution, and overall environmental improvements.

Above, a more environment-friendly and economical way to produce bleached pulp. In 2002, more than 2 million tons of brown pulp produced from wood chips were pretreated using xylanase enzyme before the bleaching process. This led to a decrease in the use of bleaching chemicals and a reduction in harmful chlorinated byproducts.



GENOMICS AND PROTEOMICS

A NEW ERA IN BIOTECHNOLOGY



THE HUMAN GENOME CONTAINS ABOUT 35,000 DIFFERENT GENES THAT COLLECTIVELY DETERMINE PROTEIN STRUCTURE, DIRECT GROWTH AND DEVELOPMENT, AND CONTROL BIOLOGICAL FUNCTIONS. OUR 'PROTEOME' IS EVEN LARGER, ENCOMPASSING ABOUT 300,000 DIFFERENT PROTEINS, WHICH SERVE AS THE STRUCTURAL FOUNDATION OF CELLS AS WELL AS THE BODY'S 'WORKER BEES'. BETWEEN THEM, THE TWIN DISCIPLINES OF GENOMICS AND PROTEOMICS ARE TRANSFORMING BIOTECHNOLOGY AT A RAPID PACE—WITH HUGE IMPLICATIONS FOR MEDICINE, AGRICULTURE, NATURAL RESOURCE MANAGEMENT, AND THE ENVIRONMENT.

CANADA IS AT THE FOREFRONT OF THIS SCIENTIFIC REVOLUTION. WITH AMPLE PUBLIC-SECTOR SUPPORT, OUR RESEARCHERS ARE PLAYING A MAJOR ROLE IN MAPPING, SEQUENCING AND CHARACTERISING THE HUMAN GENOME AND PROTEOME—AS WELL AS THE GENES AND PROTEINS OF OTHER LIVING SPECIES.

CANADIAN INNOVATION IN GENOMICS AND PROTEOMICS

Combining science, supercomputing and advanced instrumentation, MDS Proteomics can identify several hundred proteins per hour—and then decipher how all those molecules interact within the context of a cell or organism.

Montréal-based SignalGene uses proprietary drug discovery computer platforms to explore a wide range of drug candidates at a fraction of the normal cost. The firm designs compounds for a range of diseases including steroid hormone-related disorders.

The Montréal Genome and Proteomics Centre—opening in October 2002—will be one of the world's first research facilities to integrate genomics and proteomics in one cluster. This integration will help researchers cross paths and share information, leading to rapid-fire discoveries.

Caprion Pharmaceuticals Inc. creates protein maps of subcellular bodies to help detect abnormal patterns that distinguish healthy from diseased cells. This approach may lead to new ways to diagnose, treat, and possibly prevent a range of human diseases.

Tapping into Newfoundland and Labrador's stable genetic pool, Newfound Genomics Inc. analyses clinical and medical information to identify the relationship between the local population's genes and the occurrence of disease.

In the late 1980s, a major transformation in biotechnology gave birth to the science of genomics. This involved a dramatic shift from a focus on single genes to the exploration of thousands of genes, and from a molecule-by-molecule approach to a computer-aided bioinformatics approach.

Genomics is the study of genes and the role they play, individually and collectively, in determining protein structure, directing growth and development, and controlling biological functions. Human genomics includes genome mapping, gene sequencing, and functional characterization of the traits controlled by the genetic material found in human chromosomes.

The Human Genome Project, launched in the 1990s, is genomics research on a grand scale. The project's main goals are to identify all of the approximately 35,000 genes found in human DNA and determine the entire sequence of the 3 billion chemical base pairs that make up human DNA. Several types of genome maps have already been completed, and a working draft of the entire human genome sequence was announced in June 2000. As part of the global team involved in this project, Canadian scientists made a significant contribution toward mapping the genome.

Canadian researchers are now applying genomics to find better ways to diagnose, treat and prevent disease. In addition to its potential medical benefits, genomics is being used to develop: new energy sources; improved crop varieties resistant to disease, insects or drought; more nutritious foods; and healthier, more productive livestock and fish species.

While genomics is making huge strides, the science of proteomics is emerging as the next big wave in biotechnology. Proteomics involves the identification and study of the proteome—the complete set of proteins made in a given cell, tissue or organism—including their amino acid sequence, function inside cells, and interactions with each other. In humans, the proteome is much larger than the genome because a single gene may code for up to 50 different proteins.

Proteomics is essential to understanding the molecular mechanisms of disease. The key aim of proteomics in medical research is to determine how proteins behave in diseased cells versus healthy ones. Because diseased cells often manufacture proteins that healthy cells do not, every protein that is associated with a particular disease is a potential marker for diagnosis and a potential target for treatment.

In Canada, genomics and proteomics research receives broad support from all sectors. Genome Canada—a private not-for-profit corporation—works closely with partners such as federal institutions, provincial governments, the private sector, the financial community, and national and international foundations to ensure that Canada becomes a world leader in genomics research. Genome Canada funds large-scale genomics research projects in key selected areas such as agriculture, bioinformatics, environment, fisheries, forestry, health and technology development and also supports research projects aimed at studying and analysing the ethical, environmental, legal and social issues related to genomics research.

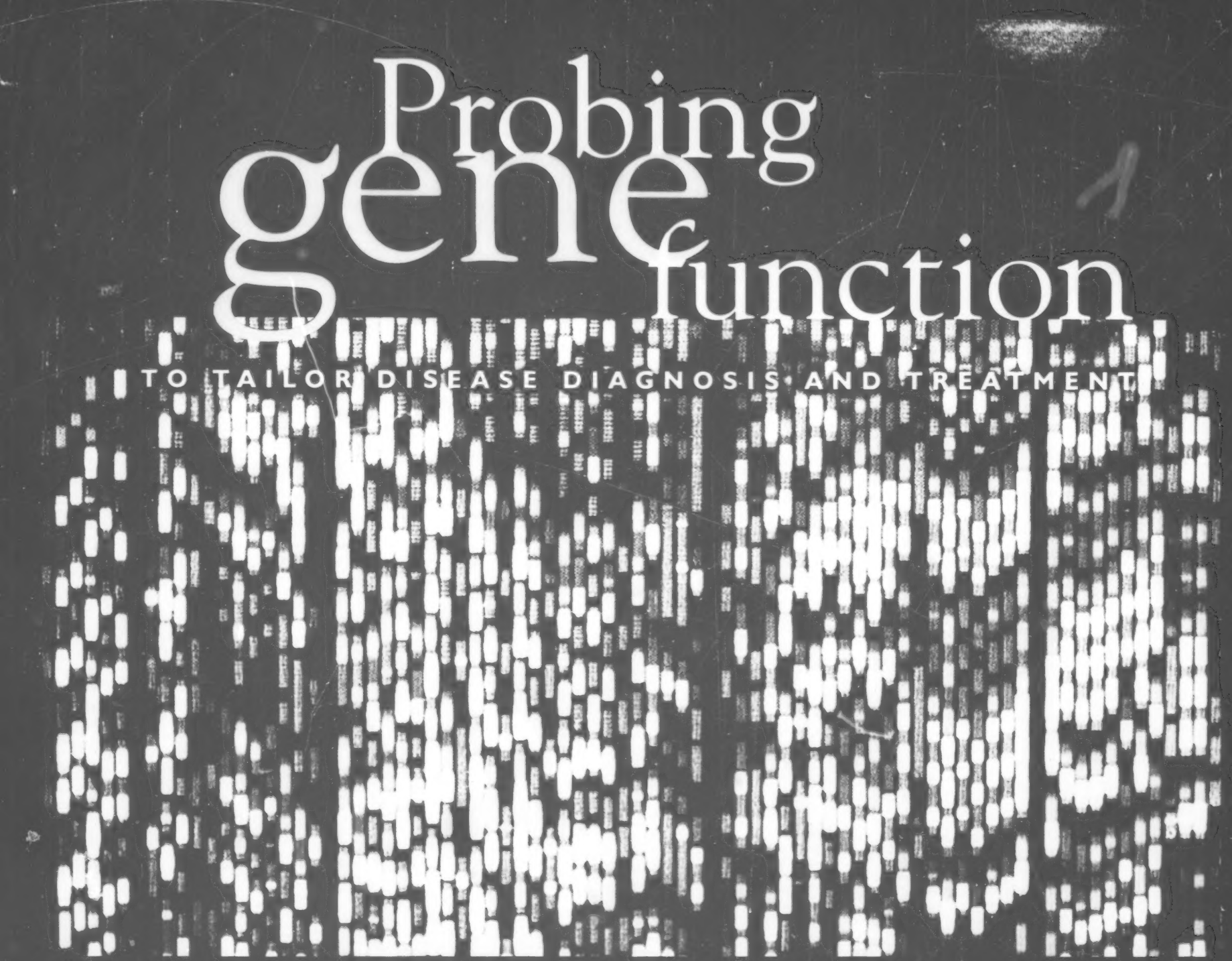
The federal government's Genomics Research Initiative provides funding for projects led by the National Research Council of Canada, Agriculture and Agri-Food Canada, Natural Resources Canada, Environment Canada, Fisheries and Oceans Canada, and the Canadian Institutes of Health Research (CIHR). Through CIHR and the Natural Sciences and Engineering Research Council of Canada (NSERC), the government also funds genomics and proteomics research at Canadian universities.

The Canadian Networks of Centres of Excellence program is a key ingredient in this support. Each network allows scientists from across the country to collaborate on research. The program includes the Canadian Protein Engineering Network, the Canadian Bacterial Diseases Network, the Canadian Genetic Diseases Network, the Canadian Network for Vaccines and Immunotherapeutics and the Stem Cell Network, among others.

Today, dozens of companies across Canada are involved in genomics and proteomics R&D. The following stories highlight some of the exciting work underway.

Probing gene function

TO TAILOR DISEASE DIAGNOSIS AND TREATMENT



ABOVE: *This image contrasts the DNA sequences of different human patients at a specific gene. Each colour represents one of the four different nucleotide bases (adenine=green, thymine=red, cytosine=blue and guanine=yellow), which make up DNA.*

THE MONTRÉAL GENOME AND PROTEOMICS CENTRE USES FUNCTIONAL GENOMICS TO LAY THE FOUNDATION FOR MEDICAL BREAKTHROUGHS.

There's strength in numbers: approximately 35,000 genes in the human genome, about 300,000 proteins in the human proteome, and now one research facility in Canada that combines the study of both.

Starting in October 2002, the Montréal Genome and Proteomics Centre will be one of the first research facilities in the world to integrate genomics and proteomics in one cluster. This co-location will allow researchers to cross paths and share information, thereby spurring each other to rapid-fire discoveries.

And in the two principal fields driving biomedical research, faster is definitely better.

With the first draft of the human genome now complete, Dr. Tom Hudson's role as Assistant Director of the Whitehead Institute/ Massachusetts Institute of Technology Center for Genome Research has come to an end. But there is still plenty to do. Aside from accepting the position of Director of the Montréal Genome and Proteomics Centre in Québec, Dr. Hudson holds the titles of geneticist, immunologist, allergist, physician, researcher and teacher.

Dr. Hudson joined the Whitehead Institute in 1991 and became leader of the team that generated the first physical map of the human genome in 1995. He also played an important role in developing the DNA chip, an exciting new technology that allows researchers to study tens of thousands of DNA samples simultaneously.

Such outstanding accomplishments made Dr. Hudson a natural choice to head the Montréal Genome and Proteomics Centre and the Génome Québec Innovation Centre, which are hosted by McGill University. After juggling multiple roles and commuting weekly between Montréal and Boston for five years, Dr. Hudson made Montréal his full-time base in 2001. By then, he had established his practice as an asthma specialist at the McGill University Research Centre and now continues his research into the genetic causes of disease and teaches in the departments of medicine and genetics at McGill University. In part, it is this degree of breadth and depth that drew Dr. Hudson back to the country.

THE WORLD OF A CELL ON A SLIDE

Imagine miniaturized laboratories the size of a postage stamp. Welcome to the amazing new world of genomics research using DNA chips.

DNA chips—also called biochips, gene chips, and DNA microarrays—allow researchers to study tens of thousands of genes in a matter of seconds. Laid out in rows and columns on a microscopic slide, the genes dot an area one-centimetre square.

Researchers expose these 'gene probes' to different biological conditions, such as a disease or a drug. Then, using a specially designed microscope, they observe which genes have been turned 'on' or 'off' as a result.

"With DNA chips, researchers are like astronauts," says Dr. Tom Hudson of McGill University. "We become observers of everything that goes on in a cell, essentially studying problems using a global approach."

The study of genomics is like popcorn: right now, we're seeing the first kernels cracking, but in 10 to 20 years, the changes will be visible to everyone.

DR. TOM HUDSON, DIRECTOR,
MONTRÉAL GENOME AND PROTEOMICS CENTRE

"Canadian scientists have had to fight to create a research environment that can compete with the United States," he says. "We've done that, and now Canada and Québec are very competitive in the area of genetics. I was anxious to come back and be part of it."

Many scientists believe the infrastructure is now in place to take a lead position in functional genomics—the quest to determine what all these sequenced genes actually do.

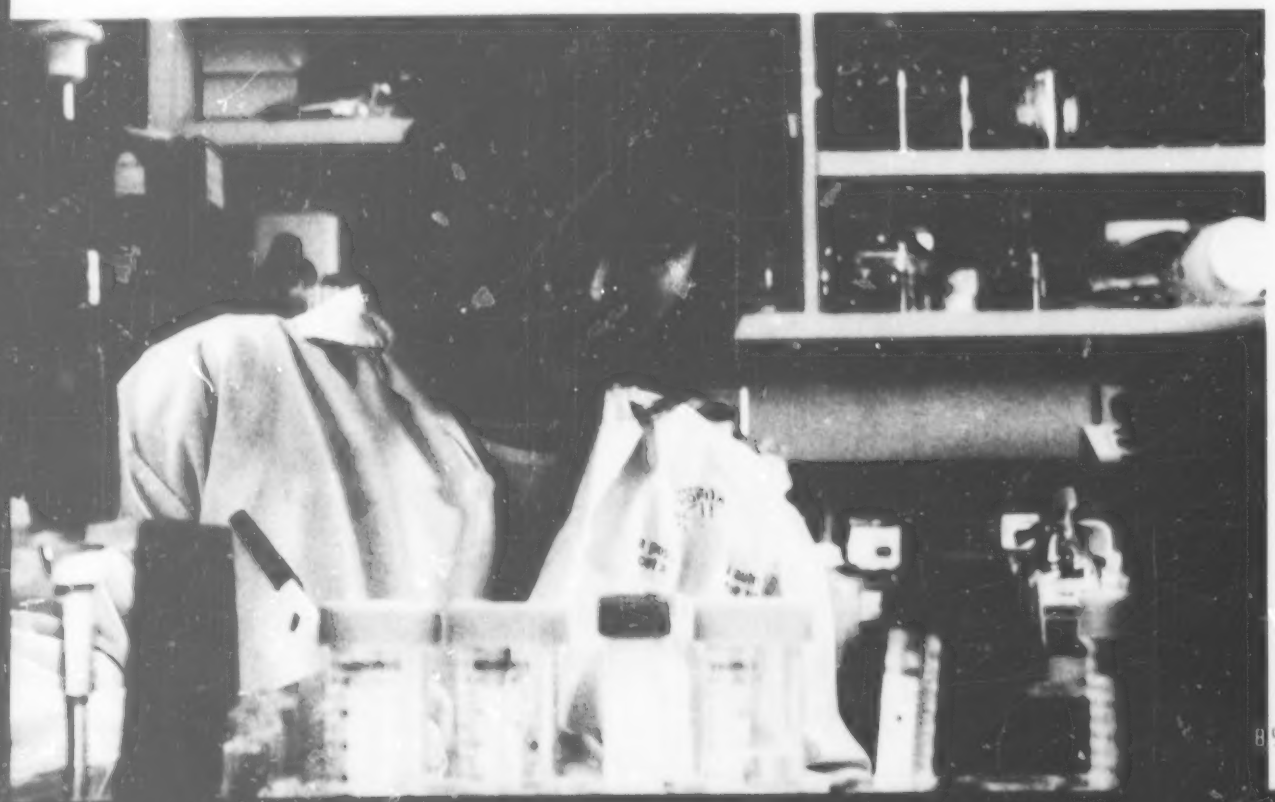
Through its research activities and strategic alliances, the Montréal Genome and Proteomics Centre will be a key component of this infrastructure. In addition to housing the technology platform of Génome Québec, the Centre will collaborate with this not-for-profit investment agency to conduct three of the 15 large-scale projects in its portfolio. These initiatives include Dr. Hudson's research on genetic regulators and haplotypes (highly structured blocks contained in the genome that explain the vast majority of all genetic variation), as well as Dr. John Bergeron's proteomic studies associated with creating cell maps, using assays to validate protein interactions, and analysing the structures of key proteins. The partnership will increase scientific contributions from Québec researchers, support economic spin-offs, and enhance Genome Canada's ability to renew and diversify its sources of funding. The joint facility will also provide vital services such as sequencing, genotyping and biochip analysis to researchers across the province, as well as throughout Canada and the United States.

When it moves into a new building on the McGill campus, the Montréal Genome and Proteomics Centre will increase its staff to 150 people. They will use genomic information to study as many as 20 major diseases, including asthma, ovarian and breast cancer, multiple sclerosis, hypertension and diabetes. Collectively, the staff will sequence large stretches of chromosomes, examine DNA markers in a large number of patients to map genetic variation, and reclassify diseases according to specific causes at the genetic level.

"Reclassification is one of the first steps that has to happen before genetics information can really affect medicine," says Dr. Hudson. "For example, where we now have asthma, we will eventually identify Type I, Type II, Type III asthma, and so on. Once we know the specific causes, we can begin to develop better, more-effective treatments."

In the Centre's future scenario, people with a particular sub-type of asthma will receive a treatment tailored to the type of disease they have. This will be a vast improvement over the current trial-and-error approach in which physicians administer various treatments until they find one that works. The ultimate winner will be the patient.

"If we can identify the underlying cause of a patient's disease through their genes, we can give them the treatment they will respond to from the first try," says Dr. Hudson. "This will be a major advance."



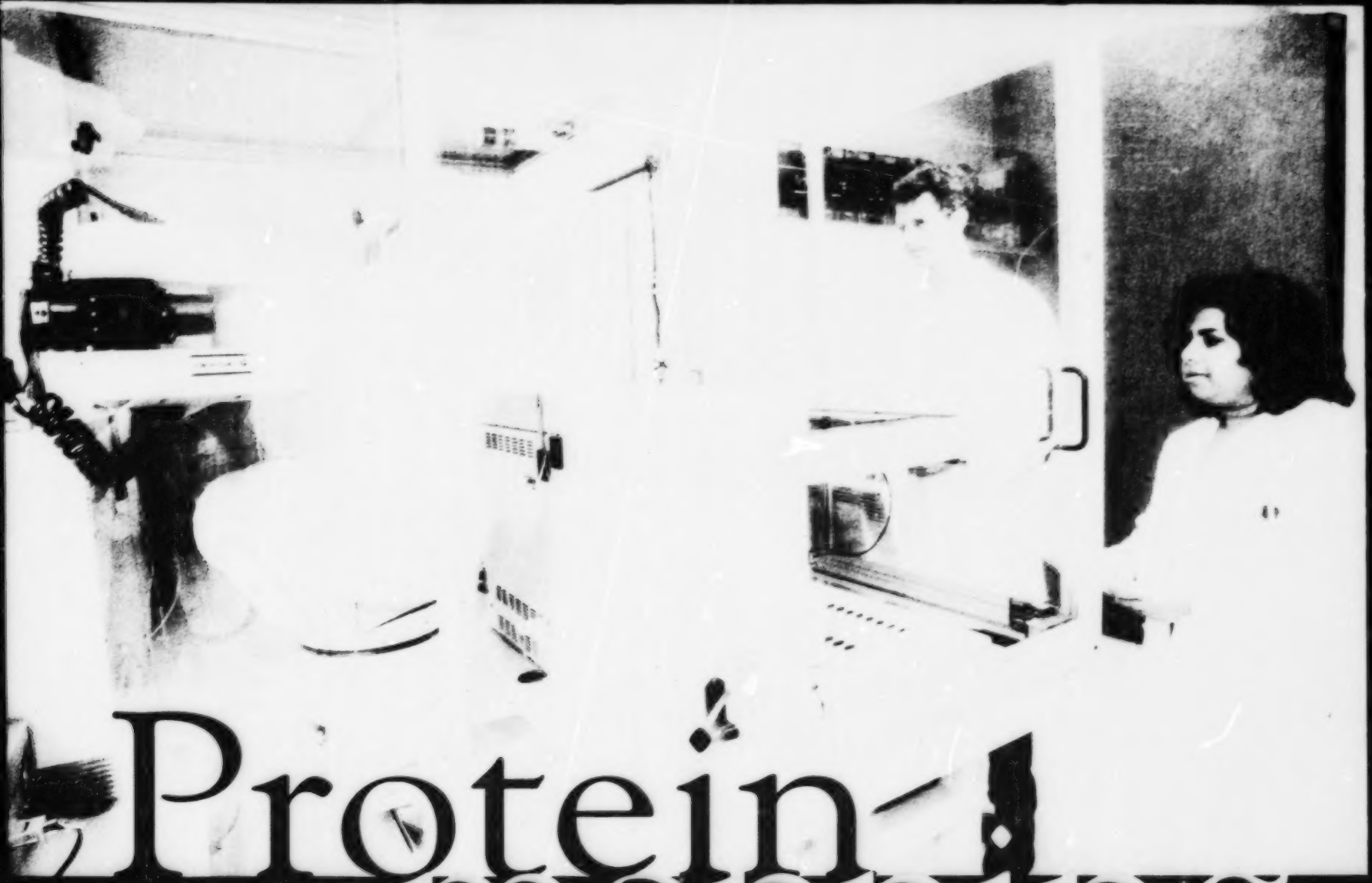
IMPROVING ACCESS TO GENOMICS DATA

Not long ago, the use of DNA chips in genomics research was limited to elite companies and organizations. Now, thanks to the Montréal Genome and Proteomics Centre, the technology is widely available.

"For the cost of making the DNA chip, any group can bring their genes here to study them using our advanced technology," says Centre Director Dr. Tom Hudson.

In 2001 alone, more than 100 groups used the service. Approximately two-thirds were based in Québec, but research centres from across Canada and the United States, and from as far away as Israel and New Zealand, also benefited.

"Our work in giving access to core facilities is as important as our research achievements," says Dr. Hudson. "We see it in the publications."



Protein mapping

PUSHES THE PHARMACEUTICAL FRONTIER

MDS PROTEOMICS INC. FUSES SCIENCE, SUPERCOMPUTING AND ADVANCED INSTRUMENTATION TO REVOLUTIONIZE DRUG DISCOVERY AND DEVELOPMENT.

Not long ago, a molecular biologist might toil meticulously for years to identify a single protein. Today, the convergence of science and technology has opened a whole new field called proteomics and set a break-neck pace for new discoveries.

By establishing a strategic alliance that provides access to one of the most powerful industrial computers in the world, MDS Proteomics is examining living matter at the protein level. The company has the capacity to identify several hundred proteins per hour—and to decipher how all those molecules interact within the context of a cell or organism.

In return, IBM gains an opportunity to showcase how its computers are able to crunch the enormous amounts of data derived from proteomics research.

Two eyebrow-raising achievements in as many months establish MDS Proteomics Inc. (MDSP) as a clear front-runner in the race to hit it big in protein-based drug discovery. The first breakthrough shows that the company is up to the task of mapping both known and unknown proteins. The second provides industry with a novel method for assessing the efficacy of drugs under development. Back to back, these feats demonstrate that MDSP is setting a grueling pace in the global competition to identify, assess and select drug targets to treat disease.

The goal of proteomics is to find out what proteins do and how they work together to make cells function in an organism. Mapping the proteome—the complete set of proteins expressed by a cell, tissue or organism—is a vital first step in the process. Proteins are prodigious multi-taskers. Many proteins perform multiple functions in the living organism and are influenced by others in their immediate environment. Without question, the task is a difficult one but the final outcome promises to make it all worthwhile. By studying the range of proteins produced by a cell, researchers can make distinctions between healthy and diseased cells, and determine the start or progression of a disease state.

Drug researchers believe that proteomics holds the key to drug development in the future.

A BLUEPRINT FOR GLOBAL INFORMATION-SHARING

Aside from its goal of being a leader in proteomic-enabled drug discovery, MDS Proteomics Inc. (MDSP) is committed to being an industry role model. The company believes in sharing the information it has uncovered to facilitate faster and more cost-effective development of new treatments for disease.

In May 2001, MDSP and IBM—in conjunction with the Samuel Lunenfeld Research Institute of Mount Sinai Hospital—launched a not-for-profit organization known as Blueprint Worldwide Inc. They also unveiled the world's first public Biomolecular Interaction Database (BIND)—a virtual home for the growing volumes of scientific information on proteins and protein interactions. The Canadian Institutes of Health Research, the Ontario Genomic Institute, and Genome Canada are also sponsors.

Pharmaceutical researchers, universities, scientists and others around the world will be able to access the database free of charge using the Internet.

ALL A COMPANY COULD WANT AND MORE

"Canada should not be modest about what it has to offer in fields like proteomics," says Mr. Frank Gleeson, President and CEO of MDS Proteomics Inc. (MDSP). "A large, well-educated workforce, world-renowned scientists, top academic and research institutes, and scientific networks of centres of excellence. All of these provide a strong infrastructure on which industry can build."

MDSP has certainly taken advantage of these assets. In November 2001, MDSP opened the world's first fully operational large-scale proteomics research facility in Toronto. The company has since recruited more than 200 employees, 70 per cent of whom are located in Canada, and established MDSP as a leader in proteomics.

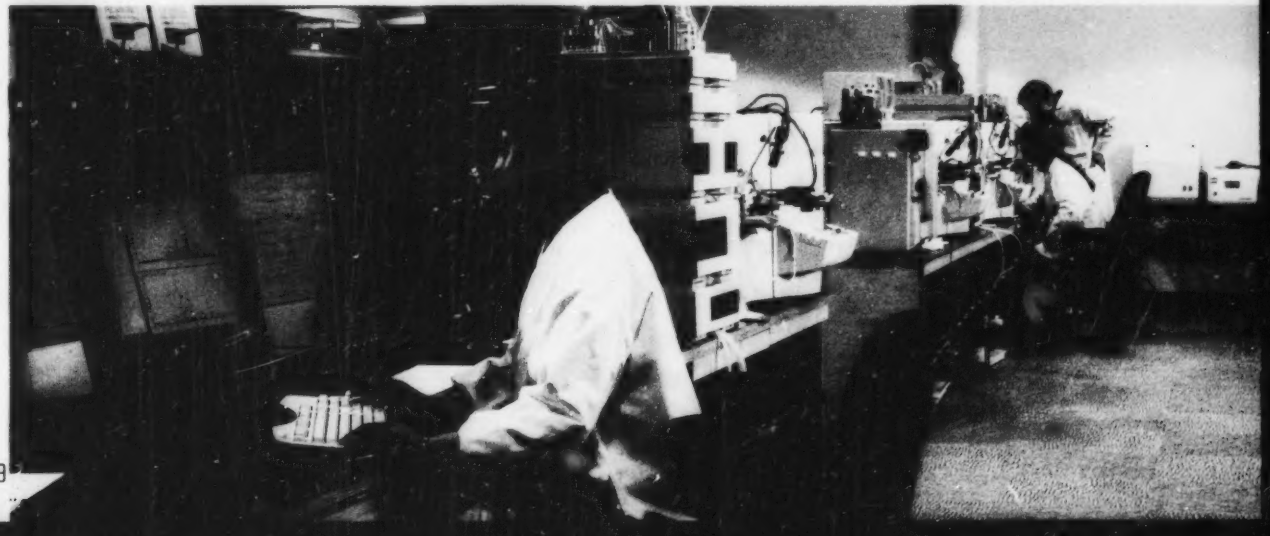
Analysis at the molecular level can help them to identify new drug targets, decide if a potential drug is effective, weed out drugs with unacceptable side effects, and even cut drug development times. Faster identification and application of more-effective treatments for cancer, AIDS, depression, diabetes and many other diseases/conditions could be the result. With such high stakes on the line, drug companies the world over are hot on the trail for new discoveries.

Established in August 1999, MDSP has literally hit the ground running and is quickly leaving major milestones in its wake. In January 2002, the company successfully applied the yeast model system to characterise 531 proteins of previously unknown function. Because the protein pathways that regulate yeast biology are analogous to those in humans, this achievement validates the company's approach to proteomic mapping and provides a framework for understanding comparable networks in human cells.

"In a matter of weeks and using only a portion of our capacity, we identified and analysed the most functionally relevant 25 per cent of the yeast proteome," says Mr. Frank Gleeson, President and CEO of MDS Proteomics.

MDSP's bioinformatics capacity includes state-of-the-art mass spectrometers capable of analysing streams of vaporized protein fragments, as well as Canada's fastest supercomputer. Built in collaboration with IBM, this 'cluster' computer can perform up to 400 million calculations per second and ranks in performance among the top 10 industrial systems of its kind in the world.

In March 2002, MDSP again used these tools to great effect. Fast on the heels of its number-crunching show of strength with the yeast proteome, the company announced a second breakthrough: the development of a novel method to determine if drugs and drug targets are effective in combating disease. By identifying the key regulatory protein 'switches' inside human cells, researchers can accurately distinguish



between healthy and diseased cells. They then can uncover the key protein targets against which new drugs will be made.

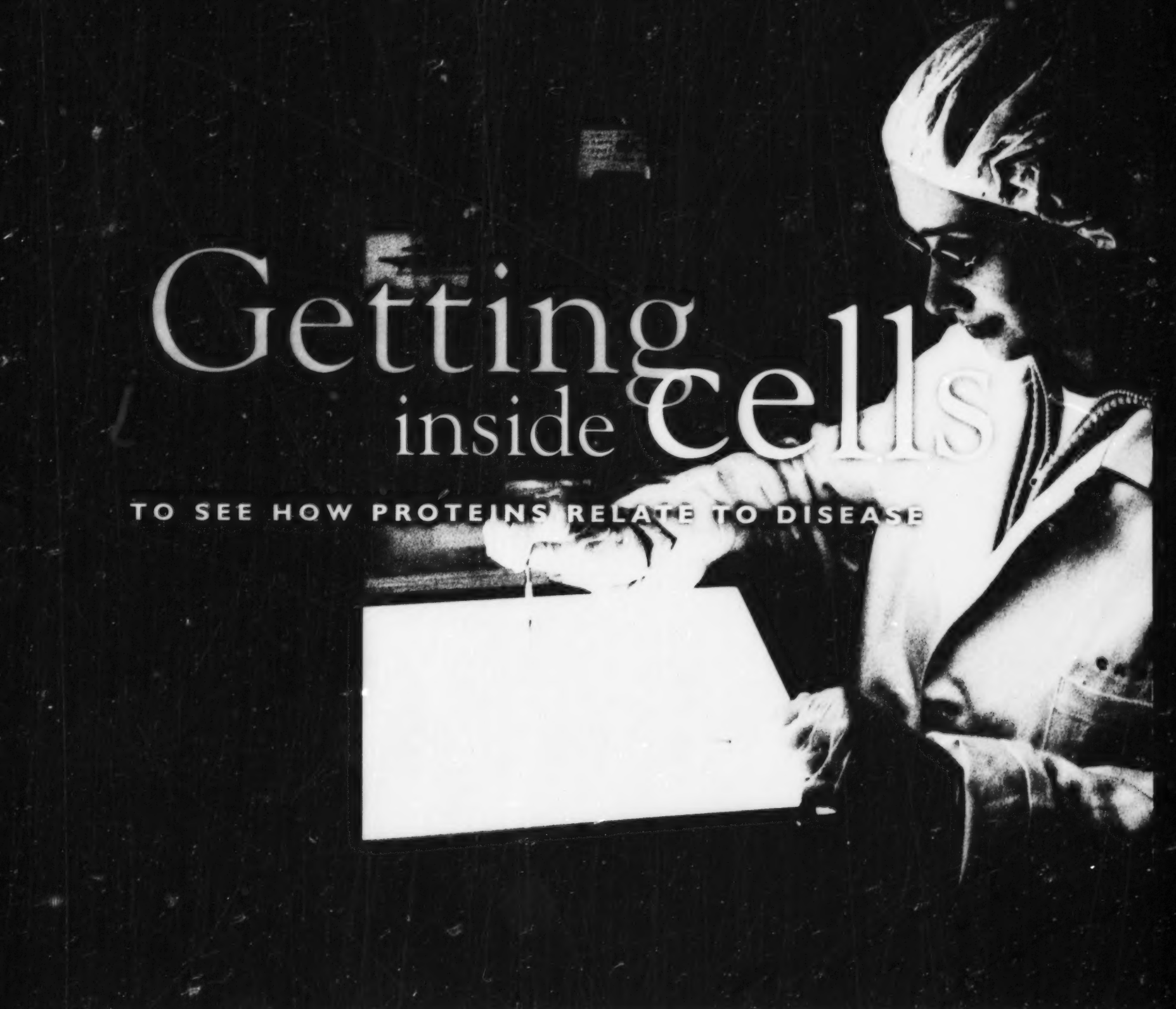
"Pharmaceutical companies spend a tremendous amount of time and money trying to determine which drug targets to advance and which to abandon early in the discovery process," says Mr. Gleeson. "This research facilitates more informed decision-making by providing a 'litmus test' for drug discovery and development."

MDSP is aiming to maintain its position at the front of the pack. The company's researchers have begun to map the proteome of the prototypical cell and plan to characterise the function of a major portion of the expressed proteins by the end of 2002. This significant feat will confirm the feasibility of proteomic mapping on an industrial scale, while also generating new protein targets for drug discovery and antibody therapies.

ABOVE: *To mine the vast amounts of data it generates, MDS Proteomics uses an IBM 'cluster' supercomputer and its proprietary bioinformatics toolset.*

Getting inside cells

TO SEE HOW PROTEINS RELATE TO DISEASE



CAPRION PHARMACEUTICALS INC. TAKES A HIGH-TECH, SUBCELLULAR APPROACH TO DIAGNOSING AND TREATING HUMAN DISEASE.

When planning a trip, it always pays to start with a map. And so it is that Caprion Pharmaceuticals Inc. is charting and redefining the frontiers of drug discovery.

The company's discovery platform, called CellCarta™, creates protein maps of subcellular bodies to help researchers detect abnormal patterns that distinguish healthy cells from their diseased counterparts.

Caprion believes this proteomics approach will lead to: new ways to diagnose, treat—and possibly prevent—a range of human diseases; and more effective drugs that target the causes, not just the symptoms.

Proteins are the building blocks of the body, giving structure to hair and bones, transporting chemicals in and out of cells, protecting vital systems and organs from foreign invaders, and facilitating chemical processes that support all aspects of life.

To date, scientific understanding of proteins is relatively limited. Beyond having a general concept of what some proteins do and evidence to suggest that much of their activity is regulated by gene expression, little is known about how they do it—or even how many proteins participate and interact in biological processes. Based on the recent completion of the human genome project with its final tally of about 35,000 genes being involved in human health, scientists estimate there may be as many as one million proteins to investigate. Clearly, there are many opportunities for cellular instructions to go awry and for protein malfunctions to occur.

Caprion Pharmaceuticals Inc. is on the case, aiming to find the most pertinent disease-related proteins and sell these protein targets to pharmaceutical companies that are keen to develop the next blockbuster treatment. Caprion has pioneered a unique approach to proteomics research that promises to unearth protein gold in the fastest, most efficient way possible.

Caprion developed a unique discovery platform, called CellCarta™, which allows researchers to understand protein function at the subcellular level. Rather than attempting to extract all the thousands of proteins from a given tissue, Caprion's approach involves examining

OPENING CELLS TO STUDY ORGANELLES

If the human body were a factory, then the cellular components called organelles represent the machinery. Each organelle has a specific role to play in the cell—the nucleus houses the genetic blueprint, while ribosomes make the proteins and mitochondria generate energy to live.

Isolating an organelle from the rest of the cell to study its function takes great skill and years of experience. Caprion's scientists are leading experts in organelle isolation using a wide variety of cell types and tissues. They have developed scalable and adaptable methods based on a variety of techniques to produce the highly purified organelle preparations needed to make protein-based disease discoveries.

IDENTIFYING NEW AGENTS OF INFECTION

Until recently, the known causes of infectious diseases were limited to viruses, bacteria, fungi and parasites. But in the process of examining a newly discovered protein-based source of infection, Caprion Pharmaceuticals Inc. is charting new market potential.

Proteinaceous infectious particles—or 'prions'—are mutant proteins believed to cause several neurodegenerative diseases. Collectively called Transmissible Spongiform Encephalopathies (TSEs), the group includes Mad Cow Disease and variant Creutzfeldt-Jacob Disease, the human equivalent.

At present, it is impossible to test for prions in humans or animals and therefore impossible to diagnose carriers of these fatal diseases. However, Caprion has developed antibodies that specifically recognize mutant prions. In partnership with Ortho-Clinical Diagnostics (a division of life sciences giant Johnson & Johnson), the company is aiming to develop the first human blood-screening test for mutant prions—and capture a stake in a worldwide market estimated at US$500 million.

the full protein complement of individual, function-specific bodies—collectively known as organelles—inside the cell. This is a level of detail often overlooked by other proteomic approaches, and an approach that achieves an unprecedented level of resolution into how proteins influence disease.

With our novel approach, our CellCarta process produces maps showing the orientation, location and movement of proteins within the cell. By focusing at the subcellular level, CellCarta detects an unprecedented number of proteins and provides unique insights into protein function relevant to drug discovery.

LLOYD M. SEGAL, PRESIDENT AND CEO, CAPRION PHARMACEUTICALS INC.

Caprion's cancer research program provides an excellent example of how CellCarta uncovers drug targets. Scientists start by analysing healthy and tumour samples from human biopsies. But instead of studying all the proteins in this cell mixture, they use specialized techniques and skills developed by Caprion to isolate, study and map specific organelles. In certain instances, such as colon cancer research, scientists may opt to focus only on the cell surface or plasma membrane from normal and tumour colon cells, which are then processed using Caprion's mass spectrometry facility and analysed by sophisticated bioinformatics programs.

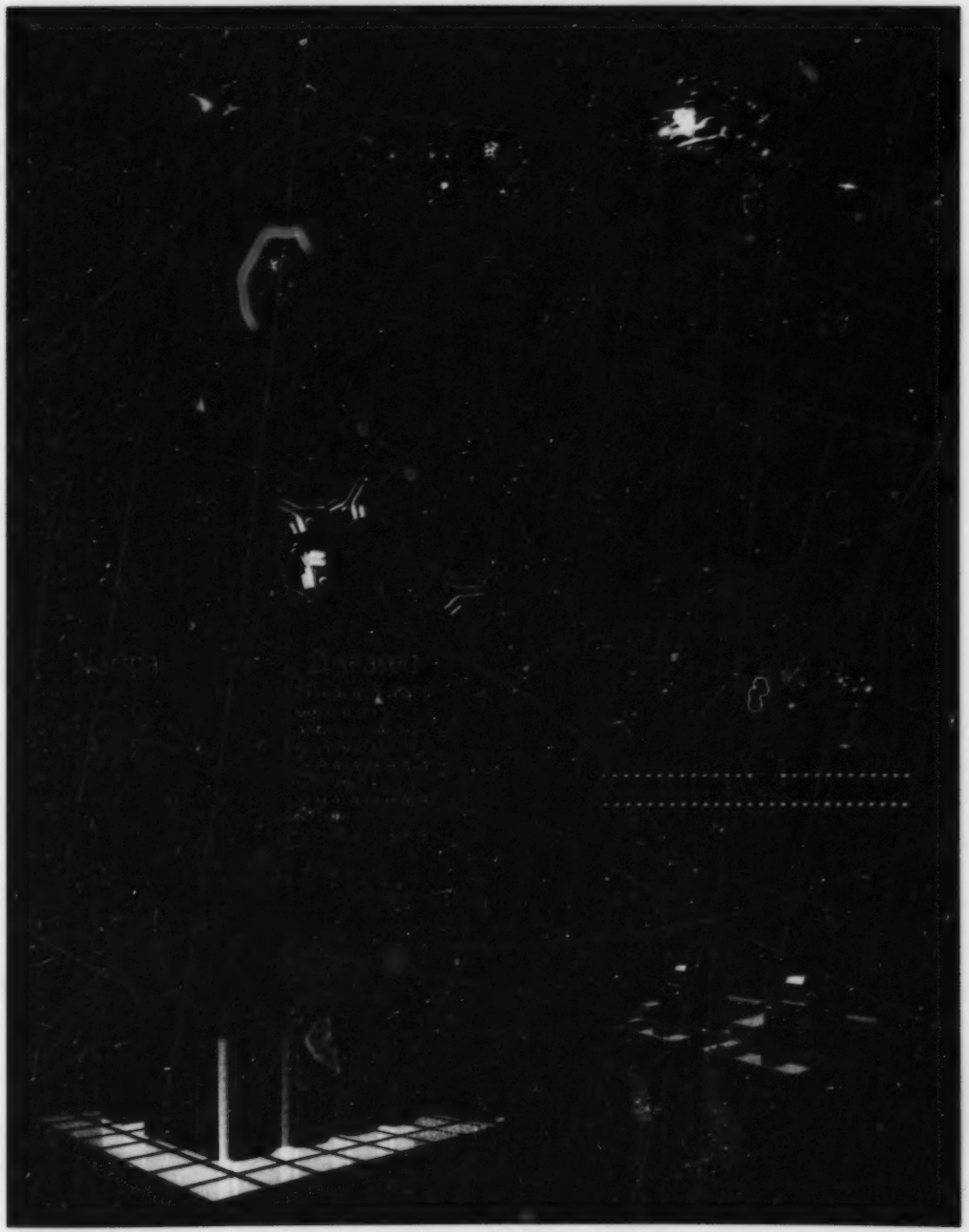
By obtaining very accurate measurements of the mass and charge ratio of molecules, mass spectrometry provides a rapid and sensitive technique for determining molecular mass and identifying protein sequences—a critical first in proteomics research. Each of Caprion's multiple mass spectrometers produces a daily volume of information that is comparable to handling and recording the call switching and billing information for six million phone customers. Clearly, the processing power is in place to deliver drug targets for the development of the next generation of products.

Not surprisingly, this targeted approach generates vast quantities of disease-relevant information—all of which must then be managed and stored. Caprion has collaborated with Sun Microsystems, Oracle Corporation, and information technology services firm CGI to create one of the world's largest dedicated protein computer farms. This cluster of high-performance servers

and storage systems can process up to 100 terabytes of information per year, the equivalent of five billion pages of information.

"Caprion has a leading technology platform combined with world-class facilities and technological infrastructure, plus strong corporate and academic partnerships," says Lloyd Segal, President and CEO. "We have all the elements required to successfully compete as a global proteomics-based drug discovery company and contribute to the advancement of medicines worldwide."

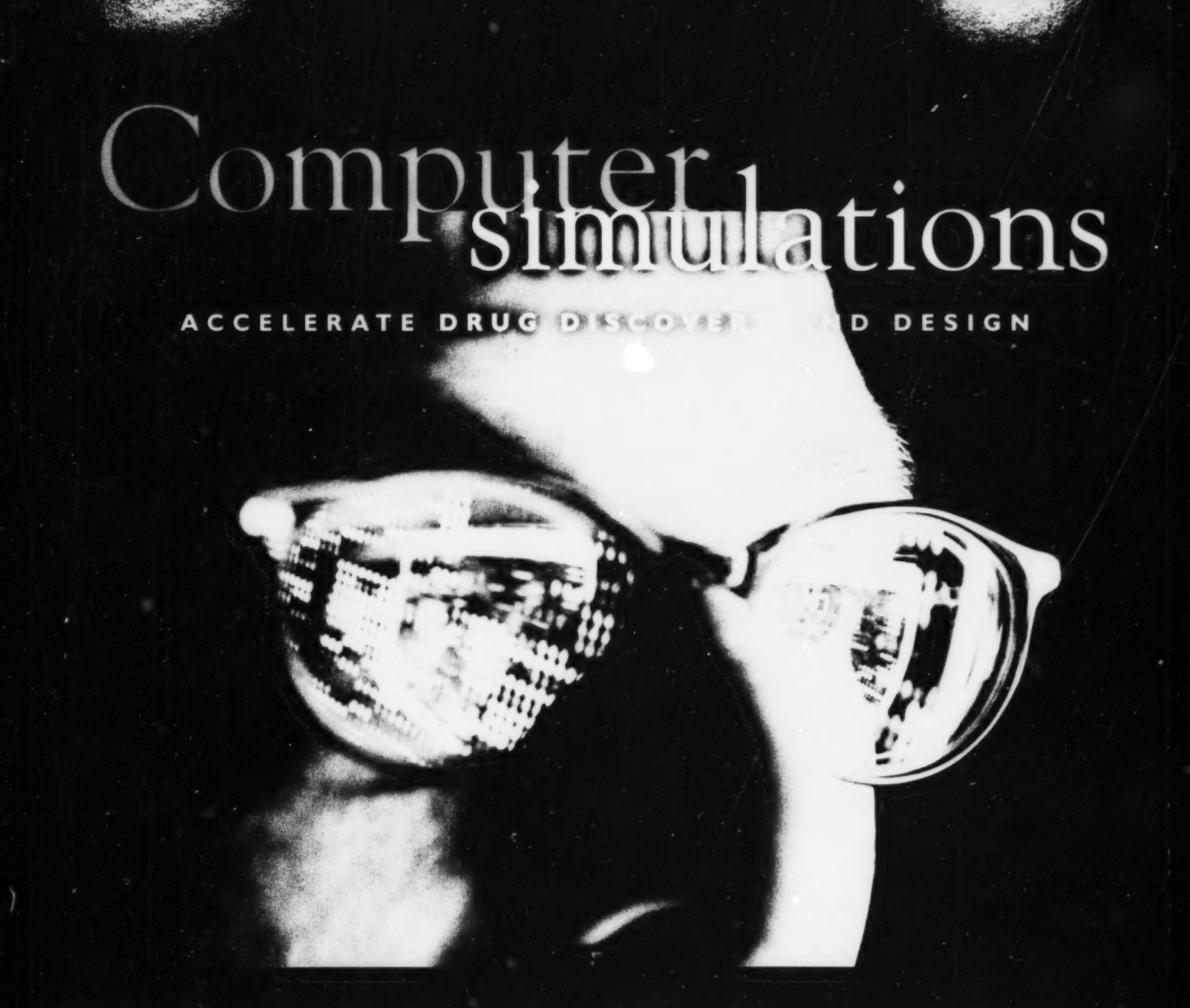
Since its founding in 1998, Caprion has: raised more than CAD$100 million in financing; attracted international experts in cell biology, mass spectrometry and bioinformatics; grown to 100 employees; and built a 54,000 square foot, CAD$31 million research facility in Montréal, Québec. On the research side, Caprion is collaborating with Micromass UK Ltd. to pursue mass spectrometry-based proteomic discoveries and with McGill University to generate innovations in organelle proteomics. The company has also established development alliances with companies such as Ortho-Clinical Diagnostics (Johnson & Johnson) and IDEXX Laboratories, a world leader in prion diagnostics.



RIGHT: *Caprion's CellCarta approach involves taking fresh human tissue samples from colon cancer biopsies (1) and using highly skilled cell fractionation (2) and organelle isolation (3) to obtain pure plasma membranes (4). The membranes are separated using two-dimensional liquid chromatography, and the membrane proteins are introduced into mass spectrometers (5) to determine protein masses and sequences. Once the data are processed (6) by custom-developed bioinformatics algorithms, CellCarta generates lists of differentially expressed protein targets. These targets, which are localised to the plasma membrane, can then be used as the basis for developing antibody-therapies (7) to treat colon cancer.*

Computer simulations

ACCELERATE DRUG DISCOVERY AND DESIGN



SIGNALGENE MANIPULATES MILLIONS OF BITS AND BYTES TO GENERATE NEW COMPOUNDS THAT TARGET DISEASE MORE EFFECTIVELY.

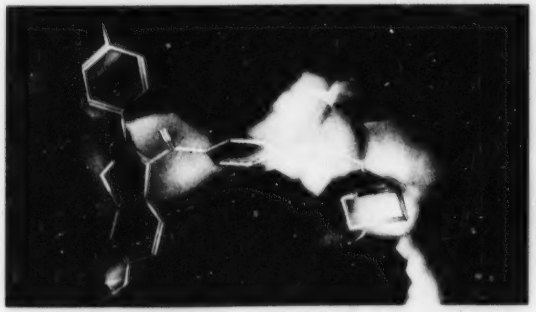
Computer-aided drug design promises to compress the time required to identify and develop exciting new drug candidates—by simulating a process that once took years of hit-and-miss bench research by medicinal chemists.

SignalGene's proprietary drug discovery computer platforms enable the company to explore a wide range of drug candidates for a fraction of the cost and time. The Montréal-based biotech firm is designing compounds that target steroid hormone-related disorders, such as breast cancer and osteoporosis, and block the formation of new blood vessels, a process that plays a major role in several diseases.

Combine powerful drug design computer software with expertise in medicinal chemistry and clinical genomics. For SignalGene, based in Montréal, Québec, these ingredients are a potent recipe to reduce the cost and time of drug discovery while improving the likelihood of success.

The key ingredient is SignalGene's discovery platform, a new information technology system that uses genetic algorithms and simulated evolutionary processes to explore clinical diversity in the development of potential drug treatments. In this case, the company is examining diseases ranging from breast cancer and osteoporosis to psoriasis and arthritis. Its proprietary technologies utilize information on the structure and activity of known pharmacologically active compounds in order to generate 'New Chemical Entities' (NCEs) that share—or improve upon—the biological activity of the original compounds.

Historically, the design of NCEs has been a long and cumbersome process requiring an average investment of six years and US$30 million per molecule. And for each compound that survives the drug development process to obtain



JOINING FORCES TO DISCOVER NEW DRUGS

Under a January 2001 technology-sharing agreement, SignalGene has teamed up with ArQule Inc., a U.S. pharmaceutical discovery firm, to develop chemical compounds that target a particular protein known to play a role in diseases such as rheumatoid arthritis.

The partners plan to generate and prioritize novel compounds based on the three-dimensional structure of p38 MAP kinase as well as on computational models of the protein's active sites, which are derived from known active compounds.

After selecting and making candidate compounds, ArQule will test their biological activity against p38 MAP kinase. In return for its involvement, SignalGene will receive research fees and other payments from ArQule.

LEFT: *Interaction of a potent anti-estrogen compound with the estrogen receptor.*

ANTI-ANGIOGENIC COMPOUND ENTERS PRECLINICAL TESTING

In January 2002, SignalGene launched animal testing of the first drug candidate from its anti-angiogenesis drug discovery program. Angiogenesis—the formation of new blood vessels—plays a major role in several diseases, especially the growth and spread of cancer. Finding ways to control this process could lead to therapeutic applications in the treatment of cancer, arteriosclerosis, retinal degeneration and some inflammatory diseases.

SignalGene's anti-angiogenesis approach is based on the design and computer-aided optimization of novel, small molecule compounds that inhibit the growth of endothelial cells, a critical step in the formation of new blood vessels. The compound selected for animal studies inhibits the proliferation of human endothelial cells and is non-toxic to cells at effective doses.

regulatory approval, nine fail somewhere along the way. SignalGene believes that its technology substantially improves these odds.

"Our expertise in computer-aided drug design and molecular modeling enables the rapid discovery and optimization of new pharmacologically active compounds, most notably in situations where sparse data exists," says Dr. Jonathan Schmidt, SignalGene's Vice President of Drug Development. "This accelerates the discovery process, while allowing us to simultaneously work in more than one area with more than one target."

SignalGene's primary research involves the development of novel targets and therapeutic approaches for diseases influenced by the steroid hormone signalling pathway. The company has established programs that explore both estradiol (female) and androgen (male) hormones, respectively known as the Selective Estrogen Receptor Modulator (SERM) and Selective Androgen Receptor Modulator (SARM) programs. In both programs, the key focus is on investigating how hormone receptors react to diverse drug candidates.

The SERM program initially seeks to identify therapies for breast cancer and hormone replacement in post-menopausal women through the design of novel, non-steroidal compounds that act against the estrogen receptor. Preclinical animal testing of proprietary compounds is already underway. SignalGene has also characterised the anti-estrogenic action, potency and specificity of two similar estrogen receptor subtypes using standard *in vitro* and cellular assays. In parallel, the company is applying its newly developed structure-based drug design technology to create additional compounds to fuel the SERM program.

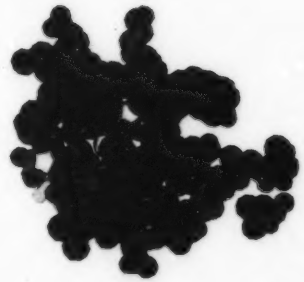
SignalGene's SARM program represents a novel area of drug discovery that targets prostate cancer, hormone replacement for men and women, and disorders associated with muscle wasting. Applying its structure-based drug design technology, this program uses the known three-dimensional structure of the human androgen receptor to design novel, small molecule compounds. The first results of synthesis and testing are expected in the second quarter of 2002.

In addition, SignalGene is developing compounds to inhibit angiogenesis—the formation of new blood vessels from pre-existing blood vessels. Angiogenesis often occurs during the growth and spread of cancers. The goal of anti-angiogenic therapy is to halt the growth of new blood vessels in order to starve a tumour of its blood and nutrient supply. Anti-angiogenic compounds may also be useful for treating other diseases such as arthritis, diabetic retinopathy, psoriasis and endometriosis.

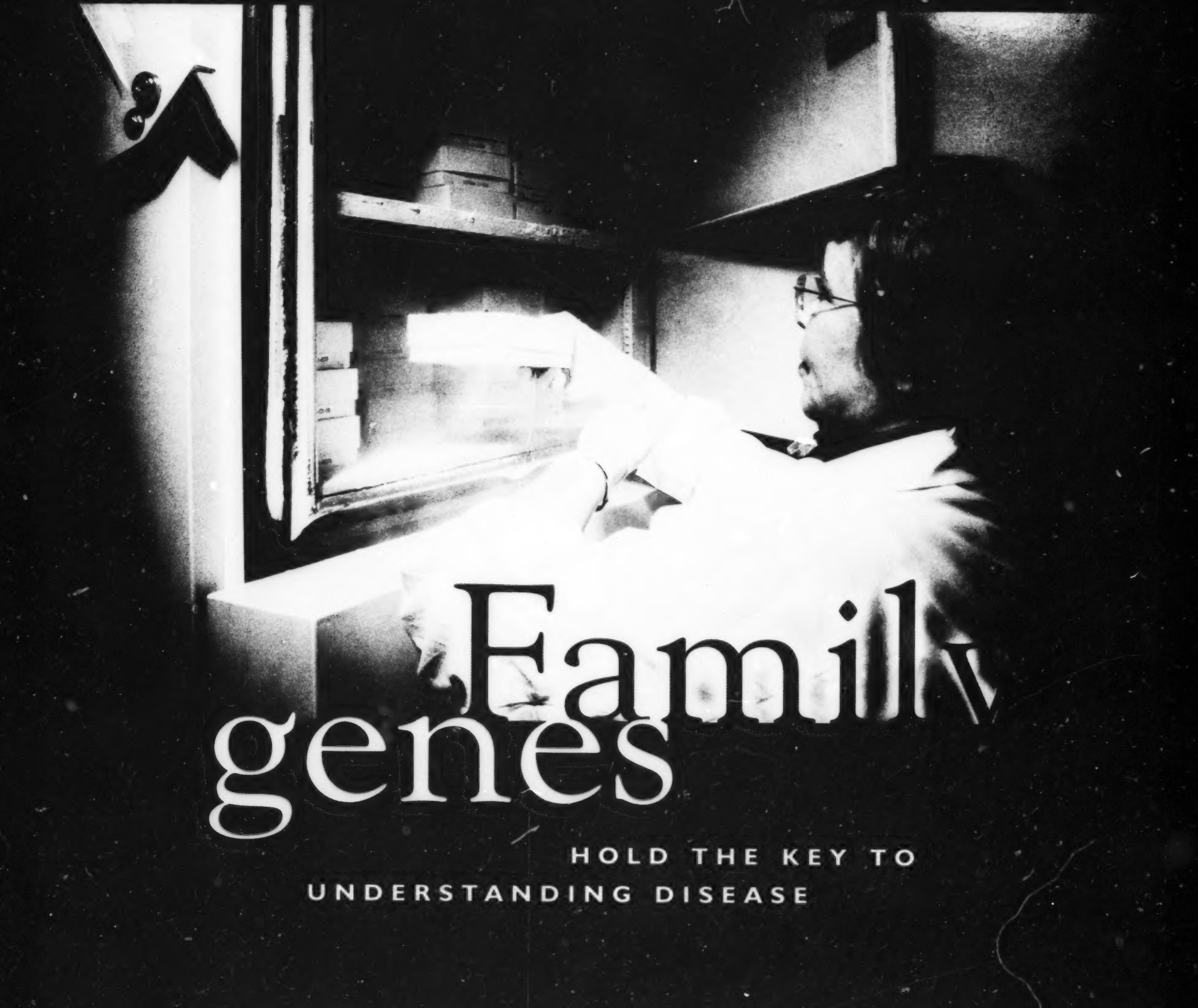
"SignalGene's unique platform for 'high throughput' discovery of disease genes, drug targets and drug candidates positions it as a next-generation drug discovery company," says Dr. Michael Dennis, President and CEO, who has spearheaded a major growth phase since joining SignalGene in 1999.

Under Dr. Dennis' leadership, SignalGene has raised a total of CAD$11.5 million from private sources. He also established six major university-hospital research collaborations and signed collaborative agreements with biotechnology companies in the United States and Europe, as well as acquiring and integrating two Canadian biotechnology firms. SignalGene's latest collaboration is a major genomics program on women's health in partnership with leading academic researchers in Québec.

A recent public share offering raised CAD$21.5 million for the company. SignalGene currently has 54 employees, 42 of whom are directly involved in drug research and development.



ABOVE: *SignalGene uses available information about the molecular structure of drug targets to design novel compounds that are easy to synthesize and have good pharmacological properties.*


Family
genes
HOLD THE KEY TO
UNDERSTANDING DISEASE

A YOUNG GENETICS RESEARCH FIRM IS APPLYING A HOME-FIELD ADVANTAGE TO EXPLORE THE RICH GENETIC POOL OF NEWFOUNDLAND AND LABRADOR.

Newfoundland and Labrador-based Newfound Genomics Inc. combines the analysis of clinical and medical information in a cutting-edge genomics laboratory to identify the relationship between the local population's genes, human health and disease. Unlike more populous parts of North America, this Atlantic Canada province has harboured a relatively stable genetic mix for centuries.

Newfoundland's genetic heritage—combined with an increased prevalence of diseases such as psoriasis and diabetes—is helping the company's research team pinpoint the genes that predispose individuals to these disorders.

The population of Newfoundland and Labrador is an important resource for genetic research. While much of North America's population growth has been based on immigration, most of Newfoundland's expansion can be traced back to a group of 20,000 to 30,000 settlers from England, Scotland and Ireland. This means the province's gene pool is relatively isolated and homogeneous—which makes it easier for researchers to identify the genes associated with specific diseases.

Established in 2000 as a clinical research company in the provincial capital of St. John's, Newfound Genomics is probing the population's genetic structure for molecular clues to help explain the increased prevalence of obesity, diabetes, osteoarthritis and inflammatory bowel disease among Newfoundlanders. Such information may lead to earlier diagnoses, better prognoses and more effective treatments for these conditions, which affect people around the world.

"We are coupling our province's rich genetic resources with core expertise in gene identification, through collaboration with Memorial University and international partners," says Dr. Proton Rahman, Chief Scientific Officer for Newfound Genomics. "As a result, we think Newfoundland and Labrador is going to make a significant contribution to the global biotechnology industry."

AN IMPORTANT RESOURCE FOR GENOMICS RESEARCH

The population of Newfoundland and Labrador is descended primarily from a limited number of founders from Ireland and southwest England. Unlike some other areas of North America, the population grew due to natural expansion rather than immigration, resulting in a 'bottleneck' population structure.

A recent study of the population's genetic architecture demonstrates a number of characteristics that facilitate the mapping of disease-related genes including homogeneity, founder effects, and an extended linkage disequilibrium—whereby two genetic markers located far apart on a chromosome are passed onto successive generations together. Because of the population's North European ancestry, Newfound Genomics' research results will be relevant and applicable to a much wider population than Newfoundland and Labrador.

STRATEGIC PARTNERSHIP BOOSTS SCIENTIFIC CAPACITY

Newfound Genomics has established a strategic partnership with Sequenom, a leading discovery genetics company. The San Diego-based company combines its high-performance technology platform, sample repository, single nucleotide polymorphism (SNP) assay portfolio and innovative strategies to determine the medical impact of genes and genetic variations.

Using a novel population genetics approach, Sequenom is systematically identifying potential disease-related genes that affect large segments of the population. Sequenom developed the MassARRAY system, one of the most powerful high-throughput genetic screening technologies in the industry.

Despite its youth, Newfound Genomics is in a strong position to map and characterise the genetic basis of target diseases. While dependent on volunteers for DNA samples, the company is staffed with local people. This natural 'home-field' advantage helps build trust and thereby facilitates the collection of donor genetic material, which Newfound Genomics stores and analyses at its multi-million dollar research facility in St. John's.

The company's efforts are also helped by the natural altruism of Newfoundlanders, who are generally quite willing to participate in genetics research. Moreover, the population is very family-oriented, and families tend to be larger than in other parts of Canada. This makes it easier to locate extended family members, who are invaluable in the conduct of genomics research.

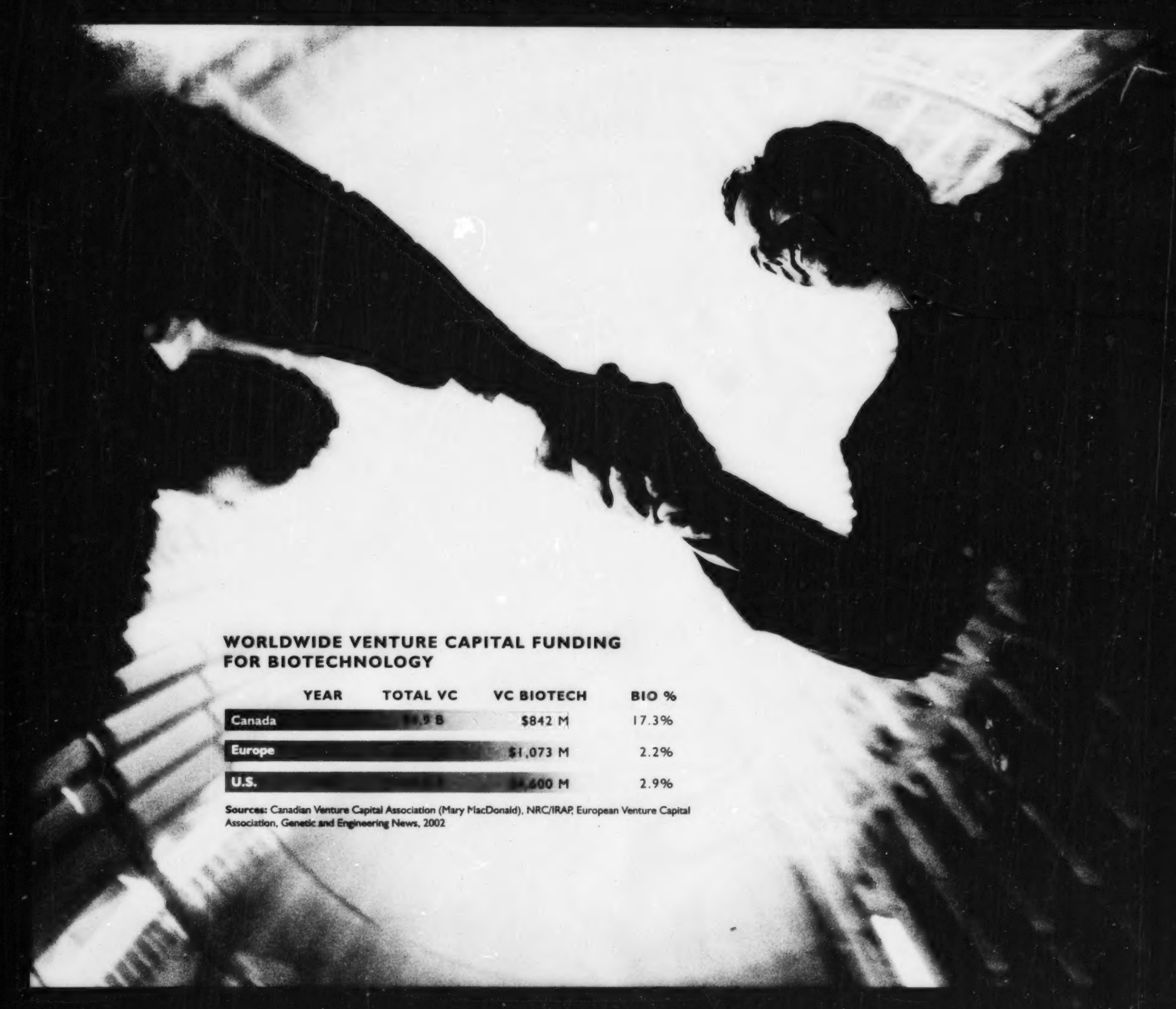
Newfound Genomics has a strategic partnership with San Diego-based Sequenom, a leading discovery genetics company, which helped fund Newfound Genomics' launch. Through this strategic alliance, Newfound Genomics enjoys access to Sequenom's disease gene discovery program, world-class standards and advanced research resources—including one of the most powerful genetic screening technologies and a library of more than 200,000 confirmed assays for common DNA variations, called single nucleotide polymorphisms (SNPs).

Newfound Genomics also has a partnership with the academic community and works closely with Memorial University of Newfoundland, which is currently developing genetics as an emerging field of excellence.

The two organizations are linked through collaborations to build research capacity, joint research initiatives, and academic development.

Newfound Genomics offers a validation program that confirms high-priority genes and/or regions of DNA. It also provides high-throughput SNP genotyping on a contractual basis. The company is currently seeking partners to broaden its novel gene discovery program.

Using the unique population characteristics of the Newfoundland and Labrador founder population as well as the company's genotyping capacity, discoveries may result in the development of drug and diagnostic tests for common complex diseases.



WORLDWIDE VENTURE CAPITAL FUNDING FOR BIOTECHNOLOGY

	YEAR	TOTAL VC	VC BIOTECH	BIO %
Canada		$4.9 B	$842 M	17.3%
Europe			$1,073 M	2.2%
U.S.			$4,600 M	2.9%

Sources: Canadian Venture Capital Association (Mary MacDonald), NRC/IRAP, European Venture Capital Association, Genetic and Engineering News, 2002

Canada...
an investment in success

CANADA'S PUBLIC AND PRIVATE SECTORS CAPITALIZE ON BIOTECHNOLOGY'S POTENTIAL

INVESTORS ARE LOOKING AT CANADA AS A KEY PLACE TO INVEST FOR BIOTECHNOLOGY. THE NUMBERS TELL A COMPELLING STORY: VENTURE CAPITAL FUNDING FOR BIOTECHNOLOGY ROSE FROM $684 MILLION IN 2000 TO $842 MILLION IN 2001.*

CANADA OFFERS A PORTFOLIO OF FINANCING TOOLS FOR BIOTECHNOLOGY, RANGING FROM ANGEL INVESTORS TO VENTURE CAPITAL TO PUBLIC SOURCES. THESE RESOURCES ARE SOLIDLY ESTABLISHED AND SUPPORT LONG-TERM GROWTH, MAKING CANADA AN IDEAL PLACE TO UNDERTAKE RESEARCH AND GET READY FOR COMMERCIAL DEVELOPMENT.

* *Source: Statistics Canada, 2002*

VENTURE CAPITAL FUNDING

Canada offers two main sources of venture capital funding for biotechnology: direct venture capital funds and labour-sponsored venture capital corporations (LSVCCs).

In addition to the funds listed below, a number of other groups have life sciences interests: the Business Development Bank of Canada, Milestone Medica of Ontario, Royal Bank Ventures, and Ventures West in British Columbia.

FUND	LOCATION	$CAD	FOCUS
BioCapital		$55 M	Human & environment
CPD Sofinov		$47 M	Multiple
Foragen		$43 M	Agriculture
GeneChem		$100 M	Human
MDS Health Ventures		$30 M	Human
MSBI		$26 M	New—links 3 universities

Source: NRC/IRAP, 2002

Labour-Sponsored Venture Capital Corporation Funds

Labour-Sponsored Venture Capital Corporate Funds (LSVCCs) are offered to individual investors, who obtain special federal and, in some cases, provincial, tax benefits. Canadians have invested more than $3.7 billion in LSVCCs. Some of these funds—which have a specific or significant investment in life sciences—are listed below:

FUND	$CAD
VenGrowth Investment Fund (I+II)	$889 M
Working Opportunity	$526 M
Working Ventures Canadian	$335 M
Canadian Medical Discoveries Fund	$351 M
University Medical Discoveries Fund	$335 M

Source: NRC/IRAP, 2002

GOVERNMENT SUPPORT

The Government of Canada is committed to creating a supportive environment for the biotechnology industry. Through a wide range of programs, the government supports research in federal organizations, universities and the private sector.

Support to federal organizations and universities

The National Research Council of Canada had the largest federal allocation to biotechnology at $83 million (out of a total budget of $640 million) in 2001-2002. Another major departmental involvement is Agriculture and Agri-Food Canada, which spent $57 million on biotech R&D in 2000-2001.

Both the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Canadian Institutes of Health Research (CIHR) support considerable levels of biotech research in universities. NSERC spent $40 million on biotech R&D in 2000-2001, while CIHR spent $133 million. Part of the funding from these organizations supports the 22 Networks of Centres of Excellence, which link university researchers across Canada. Seven of these centres are in the health sciences.

Genome Canada—a major new activity—is an arm's-length foundation with $300 million in federal funds. This support will be matched by provincial and industrial funding.

The Canada Foundation for Innovation has capital of $3.15 billion—with leverage from partners—to support infrastructure in universities. It covers a wide range of sectors, including biotechnology.

Support to the private sector

There are four main sources of federal funding available for industry:

- Technology Partnerships Canada makes strategic investments in innovative private-sector research and development initiatives. From 1997 to March 2002, TPC has approved $263 million in conditionally repayable contributions for 18 Canadian biotechnology R&D projects. These investments are supporting

development of leading-edge biotechnology applications in the environmental, medical and agricultural sectors.

- The National Research Council of Canada's Industrial Research Assistance Program provides about $5 million/year in biotechnology support to small and medium-sized firms.
- Agriculture and Agri-Food Canada's Matching Investment Initiative Fund spent $11 million in 2001-2002 on agricultural/food biotechnology research conducted in collaboration with firms.
- The Natural Sciences and Engineering Research Council's Research Partnerships Programs support academic research in collaboration with industry. Last year, the budget allocation was $117 million, of which about 20 per cent was spent to support biotechnology.

Research tax credits

Canada has one of the most extensive systems of research tax credits for industry. There is a 20 per cent federal tax credit for research and experimental development, which rises to 35 per cent for Canadian-controlled private corporations. These credits amounted to more than $1.5 billion in 2000, and a further $500 million (estimated) from the provinces.

The provincial governments also have specific initiatives to assist life sciences. One of the first was the Alberta Heritage Foundation for Medical Research (AHFMR), which was set up with a $300 million endowment from the Alberta government. AHFMR primarily funds university and hospital-based research, but some funds are also linked to industry.

In 2000, AHFMR's success inspired the Government of Alberta to create the Alberta Heritage Foundation for Science and Engineering Research. The Foundation supports 172 researchers, and the endowment is valued at $1 billion.

The province of Ontario has provided $20 million to set up or expand three technology centres in London, Ottawa and Toronto. In its 2002 budget, the province of Québec announced a new $100 million loan program to help firms access non-Québec based funds.

BUSINESS FINANCING FOR BIOTECHNOLOGY

In many countries around the world, business bio-financing peaked in 2000—and Canada is no exception. In that fiscal year alone, Canadian industry raised more than $3.3 billion. The following figures provide an overview of worldwide investment, and of Canada's place in the global scheme.

YEAR	WORLD FINANCING ($US)	CANADA %
2001 (9 months)	$10.8 B	21% (estimate)
2000	$36.0 B	9%
1999	$7.6 B	14%
1998	$6.1 B	13% (estimate)
1997	$2.6 B	9%

Sources: Biotech, BioCentury and NRC/IRAP, Nov/Dec 2001

INVESTMENT PARTNERSHIPS CANADA

Companies considering investing or expanding in Canada can benefit from Investment Partnerships Canada (IPC), which provides a wide range of assistance in assessing investment opportunities:

- Site selection data
- Advice on programs, regulations, transportation and taxation
- Introductions to key government and private-sector contacts

Through linkages with Canadian diplomatic missions around the world and investment advisors at the national, provincial and municipal levels, IPC is well positioned to assist companies in their investment decisions.

For more information:
Investment Partnerships Canada
Phone: (613) 954-5031
E-mail: invest.canada@ic.gc.ca
www.investincanada.gc.ca

APPENDIX I

The Government of Canada's Biotechnology Infrastructure

Biotechnology, with its immense promise and potential benefits, is a priority within Canada's industrial strategy. The sector's impact will be dramatic and far-reaching, with the capacity to improve human and animal health, the environment, and quality of life in general. On top of a world-class regulatory regime, the Government of Canada has developed a comprehensive strategy to maximize the benefits, and reduce the risks, that may flow from these cutting-edge technological advances. A diverse range of initiatives, undertaken by several dedicated departments, bodies and agencies, ensures that Canadian industry remains a leader in the responsible development and use of biotechnologies, now and into the future.

Companies, both domestic and foreign, are realizing the commercial benefits provided under the Government of Canada's strategy. We invite you to explore the following programs and services supporting biotechnology innovation in Canada and how they are spurring researchers, scientists and private industry to technological and commercial success.

SUPPORT FOR RESEARCH AND DEVELOPMENT

With an annual budget of $560 million, the **CANADIAN INSTITUTES OF HEALTH RESEARCH (CIHR)** is Canada's leading agency for health research. CIHR and its 13 institutes play a strategic role in building the pipeline of discovery, moving research from the laboratory to the marketplace through programs such as CIHR/SME and CIHR/R&D Research Programs, Proof of Principle and Intellectual Property Management. CIHR currently funds more than 5,000 researchers and thousands of research trainees in academic institutions across Canada. CIHR and its institutes are leading the way in building national research agendas, fostering excellence and building capacity across Canada.
For more information: **http://www.cihr-irsc.gc.ca**

GENOME CANADA is the primary funding and information resource relating to genomics in Canada. A private not-for-profit corporation, Genome Canada has received $300 million from the federal government to establish a national genomics strategy and a sustainable genomics research environment for the benefit of all Canadians. Genome Canada and its five regional centres work closely with other partners such as provincial governments, the private sector, the financial community, and national and international foundations. Genome Canada funds large-scale genomics research projects in key selected areas such as agriculture, bioinformatics, environment, fisheries, forestry, health, and technology development. It also supports research projects aimed at studying and analysing the ethical, environmental, legal and social issues related to genomics research.
For more information: **http://www.genomecanada.ca**

The National Research Council's **GENOME AND HEALTH INITIATIVE (GHI)**, in collaboration with other federal agencies, industries and universities, makes key contributions to national efforts to exploit advances in the areas of genomics and health. With an annual budget of $20 million, the GHI supports leading-edge research in agriculture, aquaculture, the environment, human health diagnostics, age-related diseases, and infectious diseases. These contributions build upon NRC's expertise in its biotechnology research institutes, as well as regional innovation networks across the country.
For more information: **http://www.nrc.ca**

THE NATIONAL RESEARCH COUNCIL (NRC) is one of Canada's most powerful resources for supporting science and technology-based innovation in every region of Canada. The Council's Biotechnology Program and Industrial Research Assistance Program make key contributions to the economy in aquaculture and marine sciences, agriculture, medical diagnostics, and health

sciences working in partnership with industry, governments and universities across the research and innovation spectrum. NRC's research-based activities are conducted by:

- The Biotechnology Research Institute
- The Institute for Biological Sciences
- The Institute for Marine Biosciences
- The Institute for Biodiagnostics
- The Plant Biotechnology Institute
- The newly created Canada-Alberta National Institute for Nanotechnology

For more information: **http://www.nrc.ca**

THE CANADA FOUNDATION FOR INNOVATION strengthens R&D infrastructure in Canadian universities and hospitals; a significant and growing portion of its $3.15 billion budget supports biological research.
For more information: **http://www.innovation.ca**

THE NETWORKS OF CENTRES OF EXCELLENCE (NCEs) represent an innovative approach to R&D by connecting, across the nation, the highest-quality research in government, university and industry in specific problem areas. Of the 22 currently funded NCEs, seven undertake work with biotech dimensions, including:

- The Canadian Bacterial Diseases Network
- The Canadian Genetic Diseases Network
- The Protein Engineering Network of Centres of Excellence
- The Health Evidence Application and Linkage Networks
- The Canadian Arthritis Network
- The Canadian Stroke Network
- The Stem Cell Network

For more information: **http://www.nce.gc.ca**

AGRICULTURE AND AGRI-FOOD CANADA (AAFC) operates 19 national research centres that act as catalysts for industry growth, providing expertise and attracting investment. AAFC and industry collaborate on more than 1,000 research projects each year, producing a steady stream of products for markets around the world.
For more information: **http://www.agr.gc.ca**

THE NATURAL SCIENCES AND ENGINEERING RESEARCH COUNCIL OF CANADA (NSERC) funds more than 9,000 university researchers every year and the advanced training of highly qualified people through scholarships and fellowships. In addition, NSERC supports innovation by sharing with industry the costs and the risks of research conducted in partnership with universities. NSERC invests over $600 million annually in university-based research in the natural sciences and engineering. It provides financial support for university research in biotechnology through discovery grants and project grants that include:

- Genomics Projects
- Strategic Projects
- Collaborative R&D
- Nanotechnology Innovation Platform

For more information: **http://www.nserc.ca**

DEFENCE R&D CANADA (DRDC), Canada's leading defence science and technology organization, provides science and technology leadership to the Department of National Defence, the Canadian Forces and the Canadian industrial base. Through its R&D programs, DRDC forges strong partnerships and collaborations with industry, government, and university partners and clients in Canada and abroad. DRDC advances leading-edge S&T expertise in three key sectors: sensors and information technology; combat systems and human systems (in particular, bio-chemical defence); and human systems integration and human system performance and protection. DRDC is a national network of five defence research centres with an annual budget of $180 million and a staff of 1,100 people.
For more information: **http://www.drdc-rddc.dnd.ca**

THE TECHNOLOGY DEMONSTRATION PROGRAM (TDP) demonstrates technologies fostered by Defence R&D Canada and Canadian industry in the context of real and potential future Canadian Forces capabilities, concepts, doctrine, operations and equipment. For more information: **http://www.drdc-rddc.dnd.ca/techdemo_e.html**

THE CANADIAN FOREST SERVICE (CFS) advances sustainable forestry in Canada and internationally by generating knowledge about, and exploring the applications of, biotechnology to improve forest regeneration and protection methods. CFS plays a key role in defining strategic research orientations, advising on environmental regulations, developing skilled workers, increasing public awareness of forest biotechnology, and coordinating activities with industry, academia, and other governmental departments and agencies.

Biotechnology research is conducted at CFS laboratories in the Pacific, Northern, Great Lakes, Laurentian, and Atlantic centres and is integrated nationwide through the **FOREST BIODIVERSITY NETWORK**, the **FOREST HEALTH NETWORK**, the **INTEGRATED PEST MANAGEMENT METHODS NETWORK**, and the **FOREST BIOTECHNOLOGY NETWORK**. For more information: **http://www.nrcan.gc.ca/cfs-scf**

CANADA ECONOMIC DEVELOPMENT FOR QUÉBEC REGIONS (CEDQ) is a key player among the federal stakeholders working for the economic development of Québec's regions. The federal agency focuses on two main areas of activity: enterprise development and improving the environment for the economic development of the regions. With its partners, CEDQ offers the following services: information, advice, skills acquisition and funding.
For more information: **http://www.dec-ced.gc.ca**

THE ATLANTIC INNOVATION FUND, administered by the Atlantic Canada Opportunities Agency (ACOA), focuses on R&D projects in the area of natural and applied sciences, as well as social sciences and the humanities where these are explicitly linked to the development of technology-based products, processes or services, or their commercialization. Focusing on small and medium-sized enterprises, ACOA's Business Development Program offers access to capital in the form of interest-free, unsecured, repayable contributions for a breadth of activities including construction, machinery and equipment acquisition, marketing, training, innovations, product/quality improvement, among others. For more information: **http://www.acoa.ca**

INVESTMENT INITIATIVES

INVESTMENT PARTNERSHIPS CANADA (IPC) is the Government of Canada's one-stop centre for investment services. IPC offers: assistance in assessing investment opportunities, including site selection data, advice on programs, regulations, transportation and taxation; or introductions to key government and private-sector contacts. Through Canadian diplomatic missions around the world, and with direct access to investment counsellors at national, provincial and municipal levels within Canada, IPC is well positioned to support companies in their investment decisions. For more information: **http://www.investincanada.gc.ca**

TECHNOLOGY PARTNERSHIPS CANADA (TPC) makes strategic investments in research, development and innovation in critical, leading-edge transformative technologies, including biotechnology and environmental technologies. TPC's risk-sharing support of R&D by enterprises in all regions of Canada leverages private-sector investments and helps accelerate the pace of innovation. TPC investments are conditionally repayable—usually in the form of royalties based on company revenues. Between 1997 and March 31, 2002, TPC approved investments of $263 million for 18 Canadian biotechnology R&D projects that will leverage $1.5 billion in private-sector innovation spending.
For more information: **http://tpc.ic.gc.ca**

THE INDUSTRIAL RESEARCH ASSISTANCE PROGRAM (IRAP) of the National Research Council of Canada provides early-stage funds to small and medium-sized enterprises. IRAP activities are distributed across Canada. For more information: **http://www.nrc.ca/irap**

THE MATCHING INVESTMENT INITIATIVE increases collaborative agri-food research activity between the private sector and Agriculture and Agri-Food Canada. The department can match up to one-for-one industry R&D contributions to collaborative research projects. For more information: **http://res2.agr.ca/research-recherche/industry/mii/match.html**

THE DEFENCE INDUSTRIAL RESEARCH PROGRAM (DIR) is a cost-sharing industrial program that promotes and improves

the research and technological capabilities of Canadian defence companies in order to strengthen the defence industrial base. DIR projects are initiated by industry and jointly funded by Defence R&D Canada and Canadian industry. For more information: **http://www.drdc-rddc.dnd.ca/business/dirp_e.html**

THE SCIENTIFIC RESEARCH AND EXPERIMENTAL DEVELOPMENT (SR&ED) Program of the Canada Customs and Revenue Agency provides financial assistance, through investment tax credits, to individuals and corporations that conduct scientific research and experimental development in Canada. The program encourages companies to do work that will lead to new, improved, or technologically advanced products or processes.
For more information: **http://www.ccra-adrc.gc.ca/taxcredit/sred/menu-e.html**

NSERC's **COLLABORATIVE RESEARCH AND DEVELOPMENT PROGRAM** shares the costs and risks with industry of collaborative research conducted in partnership with universities. The program stimulates industry investment in university research and exposes students to real-life challenges and opportunities in industry.
For more information: **http://www.nserc.ca/guide/b3_e.htm**

CIHR's **UNIVERSITY-INDUSTRY PROGRAMS** build on CIHR's research programs by facilitating strategic partnerships that better enable research to be carried through to delivery. Over the past two years, more than $110 million has been invested through these programs, stimulating infrastructure and recruitment for health research.
For more information: **http://www.cihr.ca**

THE FEDERAL GOVERNMENT'S BUDGET 2000 reduced corporate tax rates and improved capital gains as well as capital cost allowance provisions. The average corporate income tax rate is falling to 32 per cent—well below U.S. rates—while the capital gains tax rate, averaging 23 per cent, is lower than in the United States. Tax credits and accelerated R&D deductions are among the most generous in the world. Reductions in personal income tax rates, coupled with provincial cuts to both income and capital taxes, further enhance Canada's competitiveness.
For more information: **http://www.fin.gc.ca/access/budinfoe.html**

EXPORTING CANADIAN EXCELLENCE

Agriculture and Agri-Food Canada's **AGRI-FOOD TRADE SERVICE** component of Team Canada provides strategic and practical assistance to exporters of agri-food products and services to give innovative Canadian companies a competitive edge in international markets.
For more information: **http://atn-riae.agr.ca**

The **CANADIAN TRADE COMMISSIONER SERVICE** of Foreign Affairs and International Trade Canada helps Canadian companies assess their export potential and identify key international contacts, and provides them with market intelligence they need to succeed in business abroad. With a network of 500 professionals working in 140 cities around the world, the Canadian Trade Commissioner Service also provides assistance and support to international clients by matching their needs with the appropriate sources of Canadian products, services and technology.
For more information: **http://www.infoexport.gc.ca**

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Canada Economic Development
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Canadian Institutes of Health Research
www.cihr-irsc.gc.ca

Department of Foreign Affairs
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www.dfait-maeci.gc.ca

Genome Canada
www.genomecanada.ca

Industry Canada—Life Sciences Branch
Strategis.ic.gc.ca/lsb

Investment Partnerships Canada
www.investincanada.gc.ca

National Research Council Canada
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www.nrc.ca
www.nrc.ca/irap

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